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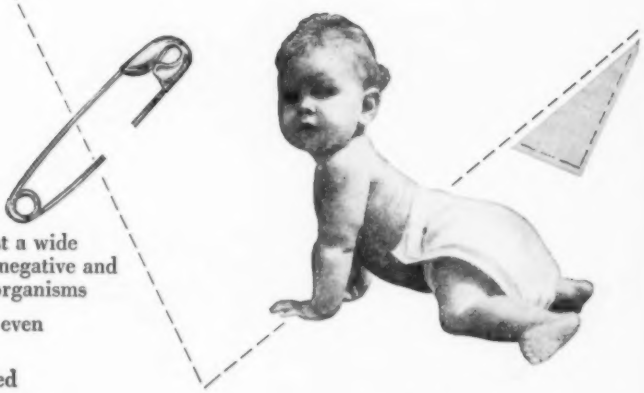

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The Journal of Pediatrics

VOL. 43 SEPTEMBER, 1953 No. 3

POST HOC, ERGO PROPTER HOC

STEWART H. CLIFFORD, M.D.*
BOSTON, MASS.

IN OUR atomic age, scientific advancements have come too fast for assimilation by us poor mortals—the only thing that apparently has not changed is human nature. In medicine, progress has been so rapid that we have become conditioned to miracles, perhaps to an extent where our common sense and critical judgment have become deadened. Yet at no time has there been more need for sound medical judgment. Many medical discoveries are reported in our newspapers and lay magazines before they appear in our medical journals. The physician must keep tuned to his radio and read the medical section of the weekly news magazines to be informed as soon as his patients concerning the latest discovery. Much of this information is factual, and, for reasons of public relations, has been released by our own medical associations and journals to the public press in advance of scheduled publication dates. This leavening with authentic information makes it easier for the lay reader and even the physician to be fooled by other medical claims and discoveries from questionable sources.

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Before discussing some of the problems that concern us today, such as the treatment of retrolental fibroplasia and the hyaline membrane syndrome and the value of Bloxsom's positive pressure oxygen air lock, it might prove of value if we paused for a moment in this hurly-burly world to consider the lessons of medical history. The accurate evaluation of systems of therapy and of therapeutic procedures is a problem that has faced succeeding generations of physicians.

One hundred eleven years ago, Oliver Wendell Holmes[1] delivered a series of lectures before the Boston Society for the Diffusion of Useful Knowledge attacking the theory and practice of homeopathy. Even at that time public relations were recognized as an important force for "some persons seem disposed to take the ground of Menzel, that the Laity must pass formal judgment between the Physicians and the Homeopathist, as it once did between Luther and the Romanists."

Holmes was confronted with a difficult situation for "when a physician attempts to convince a person, who has fallen into the homeopathic delusion, of the emptiness of its pretensions, he is often answered by a statement of cases in which its practitioners are thought to have wonderful cures."

However, he proposed "to show, by abundant *facts,* that such statements made by persons unacquainted with the fluctuations of disease and the fallacies of observation are to be considered in general as of little or no value in establishing the truth of a medical doctrine or the utility of a method of practice. . . . Those kind friends who suggest to a person suffering from a tedious complaint, that he 'had better try Homeopathy,' are apt to enforce their suggestion by adding that 'at any rate—it can do no harm.' This may or may not be true as regards the individual. But it always does very great harm to the community to encourage ignorance, error or deception in a profession which deals with the life and health of our fellow creatures. So long as the body is affected through the mind, no audacious device, even of the most manifestly dishonest character, can fail of producing occasional good to those who yield it an implicit or even a partial faith."

Holmes then organized his attack by calling on the lessons of medical history. He described "The Royal Cure of the King's Evil or Scrofula" wherein from the time of Edward the Confessor to Queen Anne, the monarchs of England would attempt to cure scrofula by touching the sufferer. Also he recalled "The Weapon Ointment"—the injured part was washed and bandaged while the weapon inflicting the wound was rubbed with the magic ointment. These two examples "illustrated how numerous facts were accumulated to prove the most fanciful and senseless extravagances."

"The Tar-water of Bishop Berkeley" was made by stirring a gallon of water with a quart of tar, allowing it to stand forty-eight hours, and then pouring off the clear water. The good Bishop recommended this concoction for the prevention and cure of all manner of disease. This "exhibits the entire insufficiency of exalted wisdom, immaculate honesty, and vast general acquirements to make a good physician of a great Bishop."

The fourth example was the "Perkins Metallic Traction Rods" that flourished only forty years before Holmes' time. The rods were two pieces of metal, one iron, one brass, about three inches long, blunt at one end, pointed at the other. They were drawn over the affected part lightly for about twenty minutes. These rods enjoyed great respect for the cure of various diseases and were to banish at least half the evils which afflict humanity. A hospital was warned that it would suffer inconvenience "unless it possesses many sets of the Tractors, and these placed in the hands of the patients to practise on each other." This example was used to show "the pretensions, the arguments, the patronage, by means of which windy errors have long been, and will continue to be, swollen into transient consequences. All display in superfluous abundance the boundless credulity and excitability of mankind upon subjects connected with medicine."

When it was said to the Perkinsists that the apparent cures were due solely to nature and whatever effects produced were merely through the imagination, the advocates came up with some reasoning that should be of particular interest to pediatricians. They contended the effects of suggestion were "sufficiently disproved by the fact of numerous and successful

cures which had been witnessed in infants and brute animals." The reply to this was that in these cases it is not the *patient* but the *observer* who is deceived by his own imagination.

> What though the CAUSES may not be explained,
> Since these EFFECTS are duly ascertained,
> Let not self-interest, prejudice or pride,
> Induce mankind to set the means aside:
> Means which, tho simple, are by Heaven designed
> T'alleviate the woes of human kind.

Only a relatively short time ago it was firmly believed that the intramuscular injection of whole blood was an effective prophylaxis against hemorrhagic disease of the newborn infant. At the present time vitamin K is generally accepted as the modern prophylactic agent to prevent bleeding in the newborn infant. In neither case was there ever a well-controlled experiment to prove the treatment's value. Advocates were so convinced on the basis of their personal clinical observations as to the effectiveness of the treatments that it would have been ethically indefensible to deprive a "control" baby of the protection. Even now voices are being raised, doubting the value of vitamin K and in another generation it may join intramuscular blood and be only of historical interest.

In 1928 convalescent serum was introduced for the treatment of acute poliomyelitis. It was considered to be of such value in reducing the incidence of paralysis that those responsible for its introduction held that it would be morally indefensible to submit a control series to the risk of developing paralysis. It took years and a great deal of courage to show that convalescent serum was of no value, in fact was harmful when given intrathecally, and that the good results obtained earlier were the result of improvements in diagnosis that enabled the diagnosis of mild preparalytic cases and their inclusion in a group that was then compared to the earlier group in which there were more severe cases diagnosed on a different basis. The studies of last summer on the effect of gamma globulin are a good example of an attempt to arrive at a sound conclusion through a sound controlled experiment. Even this study had variables present that may make the conclusions reached invalid, but at least a solid effort was made to remove the hazards of clinical observations and reach a true decision.

Perhaps retrolental fibroplasia furnishes the most dramatic modern example of "Thy wish was father to that thought." Retrolental fibroplasia, unknown until 1936, is now recognized as the most common cause of blindness in children. Many unproved ideas have been advanced as cause and cure, resulting in waves of optimism and then bitter disappointment. Exposure to light, lack of vitamin A, excessive vitamin A, lack of vitamin E, water-soluble vitamins, cow's milk, excessive oxygen have all been held responsible at one time or another for the appearance of the disease. The treatment advocated has been dictated by the theory of etiology in vogue at the moment and in addition a short but disastrous trial of ACTH and cortisone. It has been and still is almost impossible to conduct controlled experiments into the cause and treatment of this condition. The emotions of the moment are so convinced that the true

cause and treatment has been found that it would be unethical to needlessly expose a single baby to the risk of possible blindness. At the present time, one group, convinced that high oxygen is the cause, will not conduct a study giving high and low oxygen to alternate infants, while a second group, convinced that high oxygen is the cure, will not expose alternate infants to the risk of contracting the disease through depriving them of the "protection" of high oxygen.

Also current is the dictum that all infants with or prone to develop the hyaline membrane syndrome should be treated in a closed chamber receiving "fog" or "mist" in addition to oxygen. A further refinement in treatment demands that to the "mist" should be added a wetting agent of some type. The hyaline membrane syndrome, or neonatal atelectasis as it used to be called, has been recognized and treated for a long time by oxygen alone. It is a very striking syndrome in which a very sick infant may suddenly recover on or about the fourth day of the disease—the vast majority do so recover. Since adding "mist" one hospital with accurately recorded data has shown no fall in the previously established neonatal death rate, neither has there been a noticeable shortening of the course of the disease. Nevertheless the clinical impression has been and is that the "mist" is a good thing and "at least does no harm." Here again it has been impossible to set up an alternate case program to demonstrate the value, if any, of this type of therapy. Again it is the same argument, that we cannot ethically deprive the control baby of the possible benefits of "mist." Even were an alternate case study to be set up to study therapy in a condition that has a high spontaneous recovery rate, a large series of cases must be observed before the results can be interpreted as of statistical value.

To further illustrate the loose thinking that is influencing medical opinion, our leading medical journal published an article on mist plus a wetting agent[2] wherein the author reported an uncontrolled series of eighteen infants with "atelectasis or breathing difficulties of any kind" with no deaths. He compared this with forty-five babies with neonatal atelectasis from five large hospitals with twenty-nine deaths (64 per cent mortality). The unjustified assumption was that these were comparable groups of cases and that the treatment recommended was the lifesaving factor. This is not to deny that "mist" treatment may be of real value in this condition but rather to emphasize that the clinical observations on an uncontrolled series of eighteen cases cannot be accepted as evidence proving the point. The practical result has been that the general reader grasps at a cure for atelectasis thus simply afforded and the supply of the particular "wetting agent" mentioned was quickly exhausted.

In recent years exchange transfusions have been advocated in the treatment of hemolytic disease of the newborn or erythroblastosis fetalis. Those recommending this procedure, knowing well the pitfalls of clinical observations, made every effort to prove their point by statistical analyses of results in the past in groups selected to be as comparable to present groups as possible. Yet the gnawing doubt remained that in spite of everything that had been done, certain variables might be giving false conclusions.

Everything was done, that is, short of a well-controlled alternate case study. The leading advocate of exchange transfusion in this country stated,[3] "We should have liked to run a controlled experiment—but most of our patients are repeaters and come to us knowing that we will do everything we can for the children and knowing also that exchange transfusion is the method we usually use."

Mollison and Walker[4] realized that there was no general agreement on the relative value of different methods of treatment chiefly because of the failure to make valid comparisons. The comparisons that had previously been attempted covered groups of patients not only treated by different methods but also at different times. Variables such as comparative severity of the disease and factors other than the type of transfusion had not been adequately evaluated. They therefore organized a study wherein the therapy was controlled and wherein half of the infants were treated by one method and half by another, with the choice of method determined at random in advance. Fortunately the results of this study proved the unequivocal value of exchange transfusion over simple transfusion.

A new device has recently made its appearance designed for resuscitation of the newborn infant.[5] The "Bloxsom air lock" has aroused great obstetric and pediatric interest and many questions have been asked as to its value.

Bloxsom thus describes the mechanism of his method: "to provide the infant with heat, humidity, lack of handling, and oxygen and carbon dioxide pressure gradients for the favorable handling of those gases. In addition the expansion of gases is utilized for the expression of fluids and secretions in the pulmonary tree. . . . A satisfactory method of total oxygenation for the newborn asphyxiated infant has been found to occur when the infant is placed in a positive pressure oxygen air lock and the pressure cycled between 1 and 3 pounds at one-minute intervals."

The evidence submitted as to the value of the "air lock" was of two types—changes in the neonatal mortality rate and clinical observations. In the first paper 1,372 births occurred between Jan. 1, 1950, and March 24, 1950, with the "air lock" in operation, with a mortality of 14.5 per 1,000. This was compared with the experience with 6,324 births the preceding twelve months without the air lock when a mortality rate of 19.4 per 1,000 was recorded. However, in the second reported experience with the "air lock" an additional month through April 30 was included; in this month 414 births took place with a mortality of 33.8 per 1,000. When the total births of the four-month air-lock period were used the mortality was 19 per 1,000. However, now instead of comparing it with the preceding twelve months of the first paper (19.4 per 1,000) the figures for only the first four months of the preceding year were used, giving a rate of 25 per 1,000. This decrease of 25 per cent is implied as being chiefly due to the "air lock."

The evidence submitted on the basis of clinical observation was very favorable. In discussing the paper, an obstetrician of thirty years' experience testified[6]: "The lock resuscitator invented by Dr. Bloxsom is a boon to the obstetrician, the anesthetist, and

the pediatrician. I have witnessed its efficacy repeatedly—I have witnessed its marvelous achievement of resuscitating several infants and its keeping these babies alive thereafter. The change for the worse in some of the premature infants removed only for a short time from the resuscitator was so marked that no doubt was left concerning its lifesaving value. The resuscitator will perform the impossible." Another responsible observer[7] reports: "Just what our ultimate evaluation (of the air lock) will be I cannot say. It is our present impression that it is a most valuable contribution to the management of the handicapped newborn."

In spite of the fact that this device was reported in September, 1950, a careful survey of the literature fails to reveal reports of clinical results from other hospitals. In meetings of groups of pediatricians many glowing reports of the value of the apparatus, based on clinical observation, are submitted, and a few voices are raised critical of its value.

On Oct. 27, 1952, a letter was sent to the Council on Physical Medicine and Rehabilitation of the American Medical Association inquiring about the Oxygen Air Pressure Lock (Bloxsom Respirator). A reply on Oct. 30, 1952, stated that the apparatus had not yet been accepted. "In its original submission the firm claimed that the device would act as a respirator and resuscitator. After careful investigation by this Council, such claims could not be confirmed and it is felt, at the present time, that the device may have merit as an incubator; however, the Council's deliberations are not as yet concluded."

Apgar and Kreiselman[8] have recently published an experimental evaluation of the Bloxsom air lock. They reached the conclusions that, using adult depressed dogs, the only advantage of the air lock resulted from its providing a chamber with a 58 per cent oxygen atmosphere; that the air lock was unsuccessful in oxygenating and removing carbon dioxide from apneic dogs; and an analysis of other suggested advantages of the air lock could not be substantiated in respect to removal of fluid from the lungs, and the absorption of oxygen by the skin.

> In words, as fashions, the same rule will hold,
> Alike fantastic if too new or old:
> Be not the first by whom the new are tried,
> Nor yet the last to lay the old aside.
> —*Pope.*

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OBSERVATIONS ON THE EFFECT OF INDUCED HYPERGLYCEMIA ON THE GLUCOSE CONTENT OF THE CEREBROSPINAL FLUID IN PATIENTS WITH HYDROCEPHALUS

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HYDROCEPHALUS, either congenital or acquired, is frequently fatal or may leave severe permanent neurological sequelae. The incidence of hydrocephalus is probably greater than is generally realized, as some cases are so compensated that they escape clinical detection. Although the pathological changes have been well described by Dorothy Russell[1] and others, the physiopathological changes in blood-cerebrospinal fluid barrier in hydrocephalus have not been thoroughly investigated.

In order to learn more about the subject an attempt was made to find a substance that would be harmless and would pass readily from the blood into the cerebrospinal fluid. Glucose, urea, and creatinine were given by the oral route and did not appear in the cerebrospinal fluid in significant concentrations. Hypertonic solutions of sodium chloride injected intravenously failed to increase the cerebrospinal fluid chlorides. Finally, glucose given intravenously proved to be the most satisfactory substance. The passage of glucose from the blood into the cerebrospinal fluid has been studied in a group of patients on the Children's Medical Service of Bellevue Hospital and to date sixty-five tests have been carried out. This paper will be limited to our observations in ten children with congenital and acquired hydrocephalus and in a control group of thirteen children, seven with healed tuberculous meningitis and normal pneumoencephalograms and six with primary tuberculosis and no meningitis.

THE METHOD

The patient received nothing by mouth for six hours. Adequate sedation was obtained by giving phenobarbital sodium 3 to 5 mg. per kilogram one and one-half hours before the test. The hair was carefully shaved from the nape of the neck and the cisternal and lumbar areas cleaned with soap and water followed by alcohol. Glucose was then given intravenously over a two- to five-minute period, in a 25 per cent solution, in a dose of 1 Gm. per kilogram of body weight. Due to technical difficulties smaller amounts were given in two

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children, as noted later. The skin was cleaned a second time with alcohol and, with the patient in the lateral recumbent position, needles were introduced into the subarachnoid space of the cisternal and lumbar regions using careful aseptic technique. In addition, ventricular punctures were performed whenever possible. Small amounts of fluid were removed at fifteen-minute intervals (approximately ½ c.c.) over a period of two hours. Two persons were required at all times to watch the patient and to carry out the test satisfactorily. Water by mouth was offered during the test (4 to 8 oz.). The glucose determinations were made by a modified Folin-Wu micromethod utilizing 0.2 ml. of cerebrospinal fluid, adding 2 ml. of dilute tungstic acid and centrifuging to obtain a clear filtrate. One milliliter of the filtrate was placed in a 6.25 ml. Folin-Wu tube to which 1 ml. copper tartrate and 1 ml. phosphomolybdic acid reagent were added. This was boiled in a water bath for six minutes together with a blank tube containing water and a standard tube containing 0.05 mg. of glucose. The tubes were allowed to cool and then water was added to the 6.25 ml. mark. Readings were made in a Klett-Summerson colorimeter. The amount of glucose was then determined from the following formula:

$$\frac{0.05}{\text{Reading of Standard}} \times \text{Reading of unknown} \times 10 \times 100 = \text{mg. \%}.$$

Parallel blood sugar determinations were made in several instances and the usual results of an intravenous glucose tolerance curve were obtained. Because of the obvious technical difficulties these determinations were discontinued.

For the sake of brevity, the test we are describing will hereafter be called glucose test and the resulting elevations in the cerebrospinal fluid glucose will be referred to as glucose curves.

RESULTS

I. Glucose Tests in Thirteen Patients Without Hydrocephalus.—

Following intravenous injection of the specified amount of glucose, children with healed tuberculous meningitis and normal ventricles (confirmed by air studies) and children with no evidence of central nervous system disease had a consistent pattern of changing concentrations of cerebrospinal fluid glucose. This pattern was characterized by an elevation of 30 to 60 mg. per 100 c.c. of glucose above fasting levels; cisternal values were higher than the lumbar values until the last fifteen minutes of the test when the lumbar values usually rose to a level above the cisternal values. Maximum concentrations of glucose were reached between forty-five minutes and two hours.

The following patients illustrate the typical glucose curves observed in this group.

J. N. was a 14-month-old girl who had progressive primary tuberculosis and endobronchial tuberculosis with no evidence of tuberculous meningitis. The patient had been treated with streptomycin for eight months at the time of the test.

The cisternal glucose curve (Fig. 1) was higher than the lumbar curve until the last 15-minute period when the cisternal curve fell below the lumbar. Both curves rose about 40 mg. per 100 c.c. above the initial values. The maximum rise occurred more than forty-five minutes after the intravenous injection of glucose.

I. G. was a 2-year-old boy who had recovered from tuberculous meningitis. Bilateral ventriculostomy had been performed in the course of treatment; the cerebrospinal fluid had been normal for months and the pneumoencephalogram was normal.

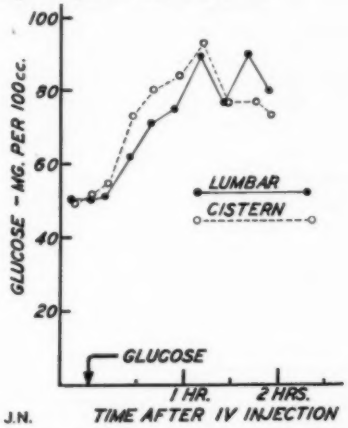

Fig. 1.—Glucose test of a patient without disease of the central nervous system. The cisternal curve is higher than the lumbar except toward the end of the two-hour period. The rise of both curves is within the normal range of more than 30 mg. per 100 c.c. and less than 60 mg. per 100 c.c.

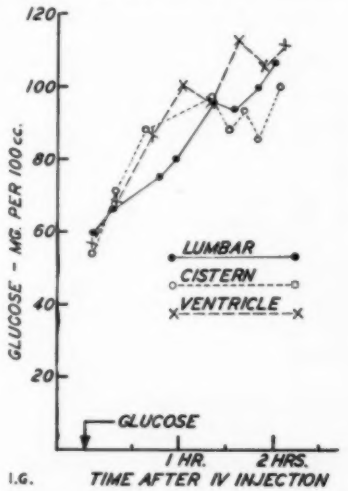

Fig. 2.—Glucose test of a patient with arrested tuberculous meningitis and no hydrocephalus. The ventricular curve is higher than the cisternal and lumbar curves. The rise of the curves is within normal limits.

The cisternal and lumbar curves (Fig. 2) resembled those of J. N. (Fig. 1) but reached slightly higher levels. The ventricular curve was higher than the cisternal or the lumbar.

II. Children With Tuberculous Meningitis and Hydrocephalus.—

A. Fatal tuberculous meningitis with hydrocephalus and block.

H. M. was a 2-year-old boy with tuberculous meningitis in a terminal stage. At the time of the test his spinal fluid was abnormal with low glucose, high protein and repeated positive cultures for acid-fast bacilli. Treatment had been abandoned one week before the test. Autopsy two days after the test revealed marked hydrocephalus and blocks due to tuberculous exudate in the lumbar and dorsal spine.

The glucose test (Fig. 3) showed a marked elevation in the lumbar curve and less marked elevation in the cisternal curve, whereas the ventricular curve failed to show a significant elevation. By significant is meant an elevation greater than 30 mg. per 100 c.c., since a minimal elevation of 30 mg. per 100 c.c. was observed consistently in the control group.

G. S. was a 9-month-old boy with active tuberculous meningitis who had received streptomycin therapy for one month. The cerebrospinal fluid showed a low glucose content, protein of over 1 Gm. per 100 c.c., and a streptomycin diffusion index* of 0.25, indicating partial spinal block. Pneumoencephalogram through the lumbar route five days before the glucose test showed marked communicating hydrocephalus. Treatment with intrathecal streptomycin was administered alternately in the ventricular, cisternal, and lumbar regions. The patient died one

*A streptomycin diffusion index[3] is the ratio of cisternal over lumbar streptomycin levels taken eight hours after the injection of 30 mg. of streptomycin in the lumbar region. Normally it should be 1.0. In the presence of partial block, the index is less than 1.0.

month after the test, after two months of treatment.

The glucose test (Fig. 4) showed a marked elevation of the lumbar glucose and a less marked elevation of the cisternal curve. The ventricular curve was flat.

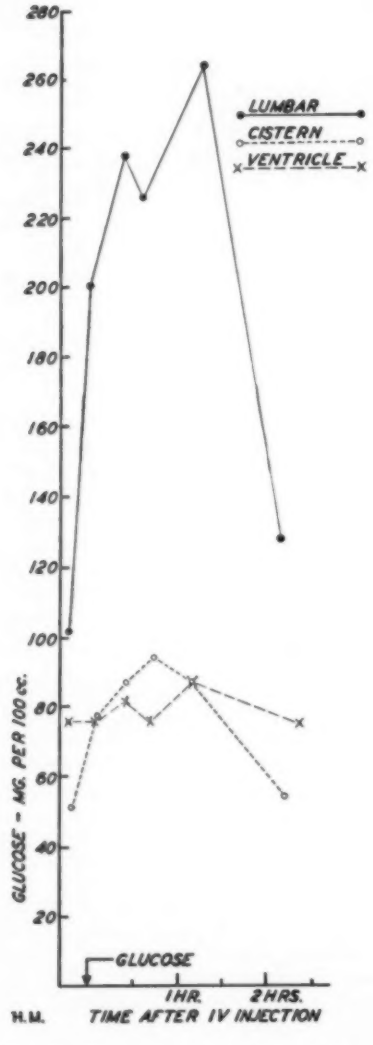

Fig. 3.—Glucose test of a patient with active tuberculous meningitis, spinal block, and hydrocephalus. The ventricular curve does not show a significant rise, but the cisternal curve shows a normal rise and the lumbar curve rises to extraordinary values.

B. K. was a 1-year-old girl with active tuberculous meningitis and evidence of enlargement of the head, i.e., separation of the sutures on skull x-ray and increase in its circumference of 2.5 cm. in sixteen days. Streptomycin diffusion index was 0.5 three days before the test, indicating a partial spinal block. Treatment with intrathecal streptomycin was being administered through the ventricular route only. The patient died after seven weeks of treatment.

The glucose test (Fig. 5) showed a pattern similar to H. M. (Fig. 3) and G. S. (Fig. 4). However, all values were lower. This may have been due to a smaller dose of glucose, as only 0.5 Gm. per kilogram of body weight was given.

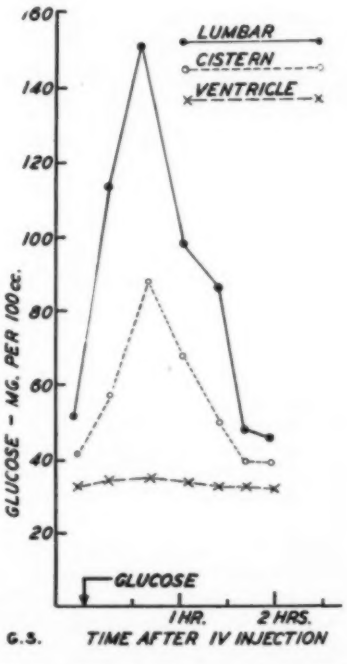

Fig. 4.—Glucose test of a patient with active tuberculous meningitis, spinal block, and hydrocephalus. The ventricular curve is flat. The cisternal curve rises to normal values, and the lumbar curve shows a marked abnormal rise.

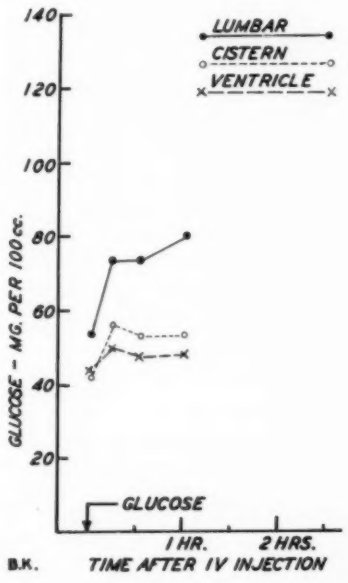

Fig. 5.—Glucose test of a patient with active tuberculous meningitis, spinal block, and hydrocephalus. This patient received half the usual amount of glucose. The ventricular curve shows only a slight rise, the cisternal curve shows a moderate elevation, and the lumbar curve is higher than the others.

B. Active tuberculous meningitis with recovery and persistent slight hydrocephalus.

L. K. was a 2½-year-old girl with active tuberculous meningitis under treatment with intrathecal streptomycin. Pneumoencephalograms one month before and one month after the first test showed moderate hydrocephalus.

The lumbar glucose curve (Fig. 6, *A*) showed a significant rise above the cisternal curve, while the cisternal curve failed to rise more than a few milligrams. This was the second patient who received only 0.5 Gm. of glucose per kilogram of body weight due to technical difficulties.

The patient made a good clinical recovery from meningitis but three months after streptomycin therapy was discontinued, pneumoencephalogram showed persistent slight hydrocephalus.

Fig. 6, *B* shows a glucose test done two months after the last pneumoencephalogram. The cisternal curve rose slightly above the lumbar after the first hour. The elevation of both curves barely reached the lower limits of the figures previously established as normal.

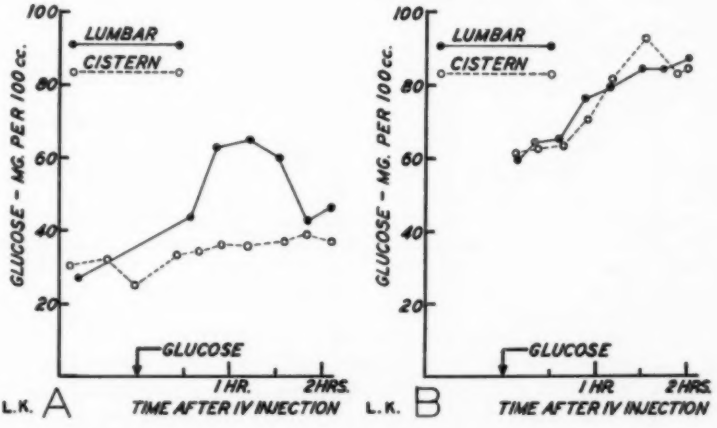

Fig. 6.—Glucose test of a patient with tuberculous meningitis and moderate persistent hydrocephalus. *A*, During therapy with intrathecal streptomycin, the lumbar curve rises above the cisternal curve. The cisternal curve does not show a significant rise. Test was performed using half of the usual amount of glucose. *B*, Five months after intrathecal streptomycin was discontinued, the lumbar and cisternal curves are about the same level. The rise of both curves reaches the lower limits of normal.

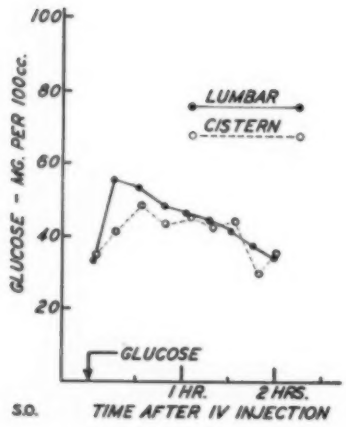

Fig. 7.—Glucose test of a patient with active tuberculous meningitis and moderate hydrocephalus who had received streptomycin by the intrathecal route, for five days. The lumbar curve is above the cisternal curve throughout most of the test. Both curves fail to show a significant rise.

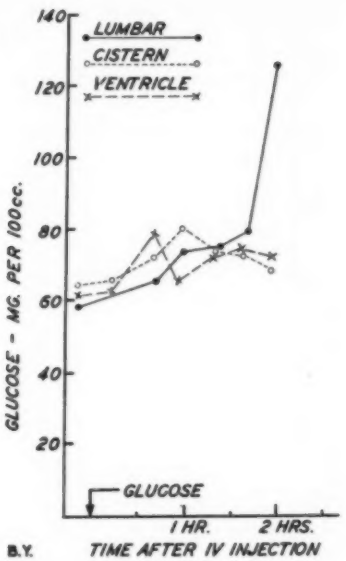

Fig. 9.—Glucose test of a patient with arrested tuberculous meningitis and marked hydrocephalus. The ventricular, cisternal, and lumbar curves are at about the same level and fail to show a significant rise except for a marked elevation of one point in the lumbar curve at the end of the test.

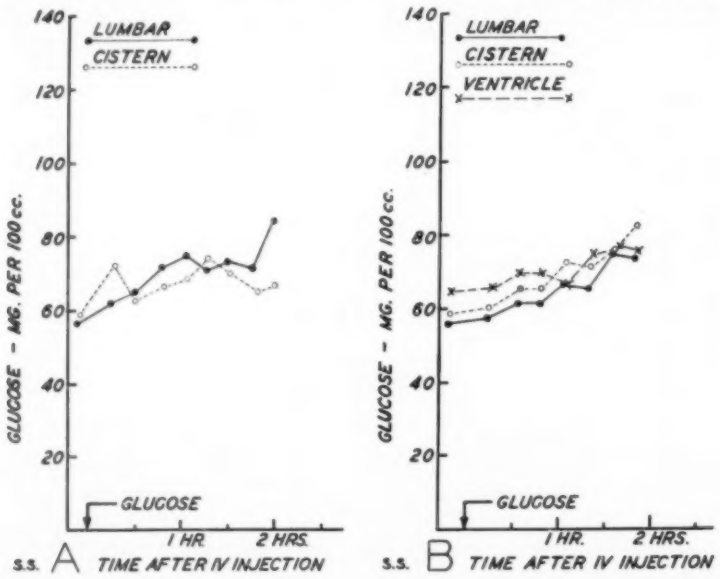

Fig. 8.—Glucose tests of a patient with arrested tuberculous meningitis and marked hydrocephalus. *A*, This test shows curves that are about the same level and fail to show a significant rise. *B*, Four and one-half months later, includes ventricular curves, shows no change.

C. Acute tuberculous meningitis with hydrocephalus, still receiving therapy.

S. O. was a 2-year-old girl with tuberculous meningitis who had received treatment with intrathecal streptomycin for five days at the time of the test. One day later the pneumoencephalogram showed evidence of a moderate degree of hydrocephalus.

Fig. 7 shows that both cisternal and lumbar curves failed to show a significant rise. The lumbar curve was slightly above the cisternal.

D. Healed tuberculous meningitis and persistent marked hydrocephalus.

S. S. was a 2-year-old girl with healed tuberculous meningitis and normal cerebrospinal fluid for eight months at the time of the first test (Fig. 8, *A*). A pneumoencephalogram performed through the lumbar route showed a marked communicating hydrocephalus. Because of persistent high cerebrospinal fluid pressure, a ventriculostomy was performed three and one-half months later. Shortly after this, the second test (Fig. 8, *B*) was performed.

Both glucose tests showed ventricular, cisternal, and lumbar curves at about the same level, failing to rise.

*B. Y.** was a 19-month-old female with healed tuberculous meningitis and normal cerebrospinal fluid for two months at the time of the test. A pneumoencephalogram three months before the glucose test had shown a very marked communicating hydrocephalus. At the time of the test the hydrocephalus was increasing and the patient was in a state of decerebrate rigidity but the cerebrospinal fluid was normal.

The glucose test (Fig. 9) showed ventricular, cisternal, and lumbar curves that failed to rise except for a lumbar rise in one point at the end of the two hours. We have no adequate explanation for this unusual behavior of the last lumbar glucose. We could discover no source of error in the procedures nor any variables that might have altered the results.

III. Children With Congenital Hydrocephalus.—

B. G. was a 6-week-old male infant with spina bifida, myelomeningocele, and marked hydrocephalus. Head circumference at birth had been 30 cm. and two days later it had increased to 37.5 cm. His head transilluminated at the time of the test.

Fig. 10 showed that the lumbar curve was above the cisternal, but neither one showed a significant rise.

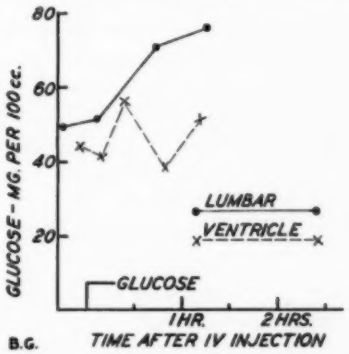

Fig. 10.—Glucose test of a patient with congenital hydrocephalus, spina bifida, and myelomeningocele. The lumbar curve is above the ventricular, but both fail to show a significant rise.

B. H. was a 7-month-old male infant who had been operated on at the age of 1 month for myelomeningocele. Following this operation he developed progressively increasing hydrocephalus. The head circumference at birth had been 33.8 cm.; at the age of 5 months it was 50 cm. A pneumoencephalogram through the lumbar route failed to fill the ventricles. Ventriculogram showed enormous dilatation of the lateral ventricles.

The glucose curves (Fig. 11) failed to show any significant elevation in the lumbar or ventricular regions.

*This patient was tested at the Babies Hospital, Columbia University Medical Center, through the courtesy of Dr. Hattie Alexander.

S. B. was an 8-month-old female infant with hydranencephalus and tremendous enlargement of the head. Occipitofrontal circumference at the age of 5 months had been 58 cm. On the day of the test she was diagnosed as having pneumococcus meningitis. Despite treatment with antibiotics she died six days later. The autopsy showed marked bilateral hydrocephalus, absence of cortex in the frontal regions, the remaining cortex being greatly thinned out. There was a grayish, slightly hemorrhagic exudate over the brain stem and part of the cerebellum. On microscopic examination there was a purulent encephalomyelitis with exudate filling the aqueduct and fibrous thickening of the choroid plexus which was probably in the third ventricle.

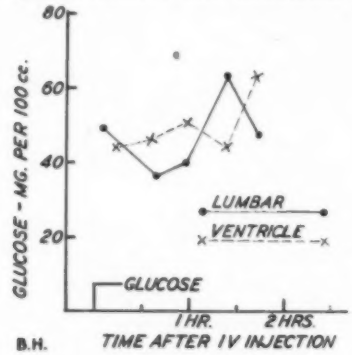

Fig. 11.—Glucose test of a patient with marked hydrocephalus and myelomeningocele treated surgically. The lumbar and ventricular curves fail to show a significant rise.

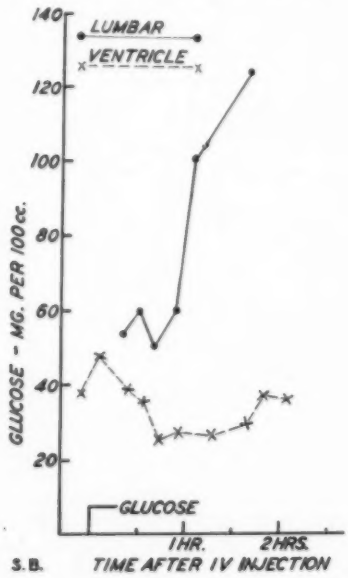

Fig. 12.—Glucose test of a patient with hydranencephaly and pneumococcal meningitis. The ventricular curve fails to rise. The lumbar curve shows a marked elevation.

The glucose test (Fig. 12) showed a ventricular curve which failed to rise, whereas there is a marked elevation in the lumbar glucose curve.

DISCUSSION

Normally an increase in the glucose concentration of the cerebrospinal fluid of the ventricular, lumbar, and cisternal regions can be produced artificially by an injection of glucose intravenously. When 1 Gm. of glucose per kilogram of body weight is injected, the rise in glucose in all portions of the cerebrospinal fluid is greater than 30 mg. per 100 c.c. above the fasting levels. But in children with hydrocephalus the concentration of glucose in the ventricular fluid following intravenous injection of the specified amount of glucose fails to increase to a significant degree, i.e., the increase is less than 30 mg. per 100 c.c. of glucose.

The pattern of the glucose curve of the lumbar and cisternal regions in a patient with hydrocephalus depends upon other conditions which may be associated with hydrocephalus. In children with hydrocephalus not associated with meningitis or with hydrocephalus and cured tuberculous meningitis, the lumbar curve fails to rise significantly. In the three children with spinal block due to exudate of active tuberculous meningitis the

lumbar curve showed a marked rise. Even in the absence of spinal block, children with hydrocephalus still receiving streptomycin intrathecally may show a significant rise in the lumbar glucose as in L. K. (Fig. 6). One infant with congenital hydrocephalus and pneumococcus meningitis also showed a significant lumbar rise. Cisternal curves in children with hydrocephalus and tuberculous meningitis with spinal block showed a significant increase in concentration of glucose except in one child who received only 0.5 Gm. of glucose per kilogram of body weight. In the two children with hydrocephalus and healed tuberculous meningitis the cisternal curve failed to rise. Cisternal curves in children with congenital hydrocephalus were abandoned because of the risk of bloody taps which occurred frequently when cisternal punctures were attempted. In all other patients cisternal punctures were easily performed.

The explanation for the flat glucose curves in hydrocephalics is not clear. It may be due to dilution of the glucose that has passed into the cerebrospinal fluid or to a failure of the glucose to pass through the blood-cerebrospinal fluid barrier. Possibly both factors may be active in some cases.

The alterations in the lumbar glucose curves of hydrocephalics with spinal block due to tuberculous meningitis might be due to a local increase in the permeability for glucose in the region of the exudate. In a similar manner the irritation of intrathecal streptomycin may produce local inflammatory reaction which increases the permeability for glucose. Friedman and his co-workers[4] have noted an increased cerebrospinal fluid glucose following administration of streptomycin by the intrathecal route; however, they believe this is not due to a "foreign body reaction" but rather to a decreased utilization of glucose by the living cell.[5] This decreased utilization of glucose may be a factor in the increased glucose values found in the cerebrospinal fluid of hydrocephalics with spinal block due to tuberculous meningitis. However, it fails to explain the rapid drop in glucose content within a period of two hours, so that the glucose values at the end and beginning of the test are approximately the same (Fig. 3). These observations cannot be explained on the basis of the present concept of the physiology of the cerebrospinal fluid formation. They suggest that under abnormal conditions there may be a local increase in the permeability of the blood-cerebrospinal fluid barrier for glucose in any portion of the subarachnoid space.

The studies of Sweet and his associates[6] indicate that more than one mechanism is involved in the production of the cerebrospinal fluid. They have shown that heavy water enters all portions of the subarachnoid space, so that it is no longer inconceivable that the constituents of the cerebrospinal fluid may be produced outside the choroid plexus.

The observations reported here were made as part of a preliminary study on the effect of induced hyperglycemia on the glucose content of the cerebrospinal fluid. The authors believe that the diffusion of glucose from the blood into the cerebrospinal fluid is a valuable means of studying the permeability of the blood-cerebrospinal

fluid barrier in normal and in abnormal conditions of the central nervous system.

SUMMARY

Tests of the diffusion of glucose from the blood into the cerebrospinal fluid have been performed in thirteen children with normal ventricles and ten children with hydrocephalus. In the former group the glucose content of the cerebrospinal fluid increased by 30 mg. per 100 c.c. or more. In the hydrocephalic children the increase in glucose content of the ventricular fluid was always below the figure established as normal. This was true of the lumbar region also, whenever the hydrocephalus was not associated with a spinal block due to tuberculous meningitis or with active meningitis.

CONCLUSIONS

1. An artificially induced hyperglycemia is followed by significant increases in the glucose content of the cerebrospinal fluid in patients free from hydrocephalus.

2. An artificially induced hyperglycemia fails to produce a significant increase in the glucose content of the ventricular fluid in hydrocephalics. This is also true of the cisternal and lumbar fields in hydrocephalics who do not have active meningitis or spinal block due to tuberculous meningitis.

3. In the presence of spinal block due to tuberculous meningitis an artificially induced hyperglycemia produces a significant elevation of the lumbar glucose curve, even when hydrocephalus is present.

4. Lumbar glucose curves in patients with spinal block, showing very high glucose content following an induced hyperglycemia, suggest that under abnormal conditions glucose may pass directly from the blood into the spinal subarachnoid space.

5. The glucose diffusion test is a useful tool in studying the blood-cerebrospinal fluid barrier.

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6. Sweet, W. H., Silverstone, B., Soloway, S., and Dewitt, S.: Studies on Formation, Flow and Absorption of Cerebrospinal Fluid. II. Studies with Heavy Water in Normal Man, Proc. Forum Sessions, 36th Clinical Congress of American College of Surgeons, October, 1950, published 1951.

OBSERVATIONS RELATED TO NEONATAL HYPOGLYCEMIA

MURDINA M. DESMOND, M.D.
HOUSTON, TEXAS

IT HAS been observed frequently that newborn infants, whether premature or full term, maintain blood sugar levels which would be considered abnormally low in older children or adults. These levels, however, must be considered physiologic, since manifestations of hypoglycemia occur infrequently in the postnatal period. Further, it has been shown at autopsy (C. Bernard, S.V.C. 1939) that glycogen may be found in the fetal liver beginning about the thirtieth week of intrauterine life. The amount increases with fetal age to term, when large amounts of glycogen are present in the hepatic parenchyma.[1, 2]

The mechanism by which hypoglycemia is maintained in the face of adequate stores of glycogen is obscure at the present time. Factors which may be contributory to the hypoglycemia are discussed in this paper. In a preliminary report[3] it was shown that newborn infants responded to epinephrine injection with rise in blood glucose. The degree of rise showed marked variation, and a tendency was present for the maximal rise to occur more slowly on the first two days of life than at the end of the first week. These observations have been extended to include: (1) the effect of increased dosage of epinephrine; (2) the response of premature infants; (3) the level of blood glycogen in newborn infants. The performance of the newborn infant subjected to the epinephrine tolerance test has been compared with the results obtained when newborn infants were subjected to the intravenous glucose tolerance tests. Last, an attempt has been made to correlate the glycemic and eosinopenic response to epinephrine.

From the Department of Pediatrics, Baylor University College of Medicine, and the Newborn and Premature Service, Jefferson Davis Hospital.

This study was aided by a Fellowship from The National Foundation for Infantile Paralysis, Inc.

SUBJECTS AND METHODS

Methods.—Blood obtained by heel prick was utilized for determination of glucose according to the method of Lauber and Mattice,[4] a method which gives "true glucose" values. The number of circulating eosinophils per cubic millimeter of blood were counted according to the method of Randolph,[5] using the Fuchs-Rosenthal counting chamber (0.2 mm. depth). Heparinized plasma was used for the determination of blood glycogen and inorganic phosphorus; the former, according to the method of Wagner,[6] and the latter, the method of Fiske and Subbarow.[7]

Subjects.—The subjects in this study were normal newborn full-term and premature infants in the nurseries of Jefferson Davis Hospital.

The nursery feeding routine for full-term infants is as follows: Nothing is offered by mouth for twelve hours, boiled water is given at four-hour intervals for the succeeding twelve hours, to be followed at twenty-four hours by either breast feeding or formula. The newborn formula con-

sists of two parts of water to one part of evaporated milk, with 5 per cent by volume added carbohydrate. Premature infants are offered nothing by mouth for the first twenty-four hours, 5 per cent glucose in boiled water for the next twelve hours, to be followed by gradually increasing amounts of a high-carbohydrate, high-protein, low-fat formula "Dalactum."

Before the epinephrine or glucose tolerance tests, a water feeding was substituted for a regular feeding if the infant were less than 24 hours of age. The interval between the last milk feeding and the beginning of the test in premature infants was approximately a six-hour period. The glucose solution used (10 per cent in distilled water) was obtained from freshly opened 5 c.c. ampules and given into a scalp vein over a three- to four-minute period.

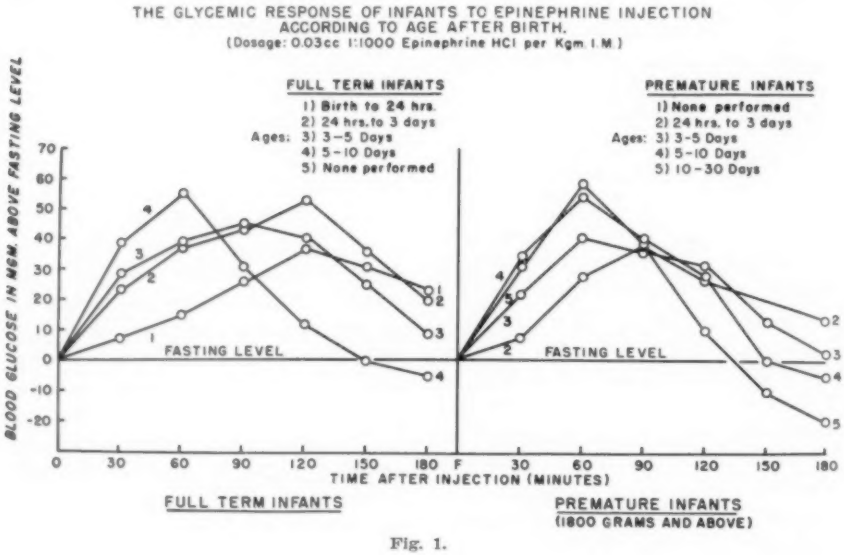

THE GLYCEMIC RESPONSE OF INFANTS TO EPINEPHRINE INJECTION
ACCORDING TO AGE AFTER BIRTH.
(Dosage: 0.03cc 1:1000 Epinephrine HCl per Kgm. I.M.)
BLOOD GLUCOSE IN MGM. ABOVE FASTING LEVEL
FULL TERM INFANTS
1) Birth to 24 hrs.
2) 24 hrs. to 3 days
Ages: 3) 3-5 Days
4) 5-10 Days
5) None performed
PREMATURE INFANTS
1) None performed
2) 24 hrs. to 3 days
Ages: 3) 3-5 Days
4) 5-10 Days
5) 10-30 Days
FASTING LEVEL
FASTING LEVEL
TIME AFTER INJECTION (MINUTES)
FULL TERM INFANTS
PREMATURE INFANTS
(1800 GRAMS AND ABOVE)

Fig. 1.

TABLE I. THE GLYCEMIC RESPONSE OF INFANTS TO EPINEPHRINE INJECTION (0.03 C.C. 1:1,000 EPINEPHRINE HYDROCHLORIDE, INTRAMUSCULARLY)

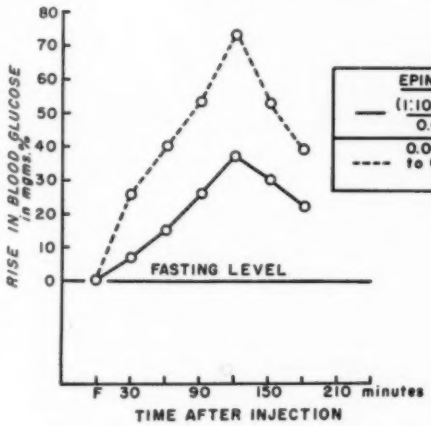
	FULL-TERM INFANTS					PREMATURE INFANTS (BIRTH WEIGHT OVER 4 POUNDS)				
		FASTING BLOOD SUGAR LEVEL		MAXIMAL RISE ABOVE FASTING LEVEL			FASTING BLOOD SUGAR LEVEL		MAXIMAL RISE ABOVE FASTING	
AGE AFTER BIRTH	NO. OF CASES	MEAN MG. %	STAN. DEV. MG. %	MEAN MG. %	STAN. DEV. MG. %	NO. OF CASES	MEAN MG. %	STAN. DEV. MG. %	MEAN MG. %	STAN. DEV. MG. %
Birth to 24 hr.	14	48	±12	51	±16	–	--	--	--	--
24 hr.-3 da.	7	50	±14	53	±24	8	47	±14	41	±18
3-5 da.	8	55	±12	48	±17	7	51	±10	53	±29
5-10 da.	8	72	±15	57	±16	7	64	±16	57	±33
10-30 da.	--	--	--	--	--	9	70	±17	55	±15

THE GLYCEMIC RESPONSE TO EPINEPHRINE INJECTION

Epinephrine (0.03 c.c. per kilogram 1:1,1000 epinephrine hydrochloride) was given intramuscularly to thirty-seven full-term infants and thirty-one premature infants weighing between 1,800 and 2,500 grams at birth. Samples of capillary blood for blood glucose determinations were taken from the heel before and for thirty-minute intervals over a three-hour period following the injection. The rises obtained in blood glucose levels are summarized in Fig. 1 and Table I. The glycemic response is tabulated according to age after birth in both groups.

All groups show a response to epinephrine with a rise in blood glucose. The height of rise above fasting level shows marked variation within each group as may be seen in the large standard deviations from the mean. The lowest average rise (41 ± 18 mg.) is seen in the youngest premature group, while the highest (57 ± 16, 57 ± 33) is seen in the 5- to 10-day-old group in both premature and full-term infants. These differences are not significant. The rise of blood glucose in the latter groups is comparable to that found by Livingstone and Bridge[8] in infants aged 3 to 22 months. While the height of glycemic response does not significantly change with age after birth, the timing of the rise in blood glucose shows a consistent change with age. In both premature and full-term infants the glycemic response becomes more prompt during the first week of life, as does the return toward fasting level.

EPINEPHRINE TOLERANCE CURVES OF NEWBORN INFANTS.
EFFECT OF INCREASED DOSAGE OF EPINEPHRINE.
(Term infants less than twenty-four hours of age)



EPINEPHRINE DOSAGE	NO. CASES	RISE IN BLOOD GLUCOSE mg %
—— (1:1000 Epin. HCl) 0.03cc/kg. I.M.	14	51 ± 16
---- 0.06/kg. I.M. up to 0.18 cc. total dose	13	76 ± 22

Fig. 2.

A group of thirteen normal full-term infants less than 24 hours of age were given a larger dosage of epinephrine (0.06 c.c. per kilogram 1:1,000 epinephrine hydrochloride, intramuscularly, up to 0.18 c.c.) and the changes in blood glucose level followed over a similar three-hour period. The glycemic response of full-term infants less than 24 hours of age to the larger

and smaller dosages of epinephrine, are compared in Fig. 2. The mean rise in blood glucose with the larger dosage (76 ± 22) is approximately 50 per cent higher than that obtained with the smaller dosage (51 ± 16). This difference is significant.* The peak response comes at approximately two hours after injection in both groups.

Thus, during a period in newborn life when the blood sugar level is low, a temporary rise in the level may be obtained by the injection of epinephrine. The degree of rise roughly follows the dosage given. If the action of epinephrine is truly glycogenolytic, then the liver must be presumed to contain glycogen, even when the peripheral blood glucose level is low by adult standards.

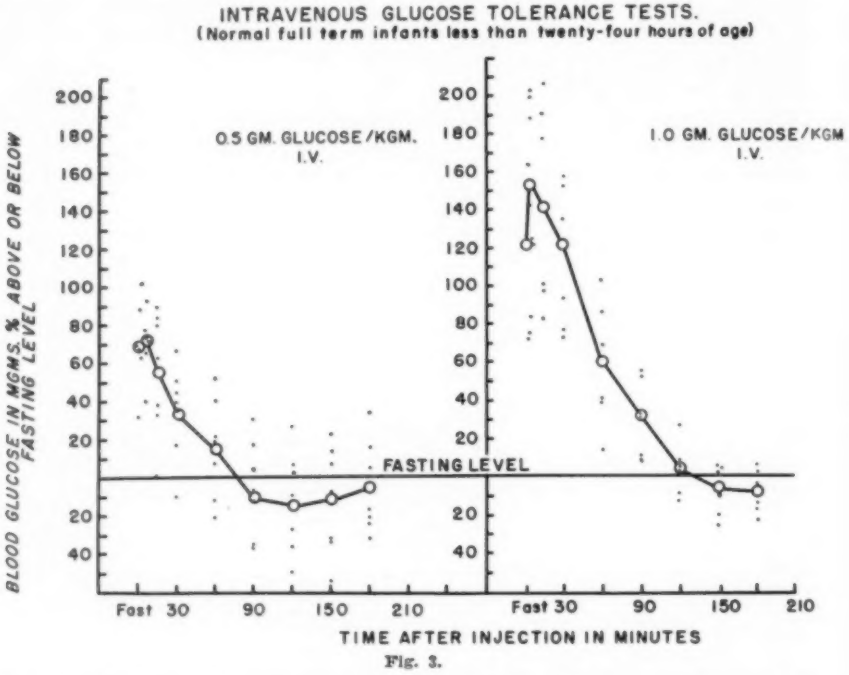

INTRAVENOUS GLUCOSE TOLERANCE TESTS.
(Normal full term infants less than twenty-four hours of age)
0.5 GM. GLUCOSE/KGM. I.V.
1.0 GM. GLUCOSE/KGM I.V.
BLOOD GLUCOSE IN MGMS. % ABOVE OR BELOW FASTING LEVEL
FASTING LEVEL
Fast 30 90 150 210
TIME AFTER INJECTION IN MINUTES

Fig. 3.

TABLE II. INTRAVENOUS GLUCOSE TOLERANCE CURVES IN NORMAL NEWBORN INFANTS LESS THAN TWENTY-FOUR HOURS OF AGE

DOSAGE GLUCOSE PER KILOGRAM I. V.	NO. OF CASES	AVERAGE AGE IN HR.	AVERAGE WEIGHT IN GRAMS	FASTING LEVELS MG. GLUCOSE %	PEAK RISE IN BLOOD GLUCOSE IN MG. %	REDUCTION IN URINE (BENEDICT'S)
0.5	7	11	3,289	54 ± 15	79 ± 16	0 to 1+
1.0	6	14	3,374	47 ± 6	159 ± 45	0 to 4+

*$t = \frac{M_1 - M_2}{S\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} = 3$

INTRAVENOUS GLUCOSE TOLERANCE TESTS

Intravenously injected glucose was given to full-term and premature in-

fants in order to determine whether the newborn infant with its hypoglycemic tendency responded to injected glucose early in life any differently from older infants and adults.

Glucose was given to newborn full-term infants less than 24 hours of age in two dosages: (a) 0.5 Gm. per kilogram of body weight, and (b) 1.0 Gm. per kilogram of body weight. Blood glucose levels were checked over a three-hour period. Composite and average curves are shown in Table II and Fig. 3. Using either dosage the resulting average curves are within normal adult limits. With the standard dosage of 0.5 Gm. glucose per kilogram, intravenously, the descending limb of the curve comes back to the fasting level between sixty and ninety minutes, falls into a period of deeper hypoglycemia with a tendency to return toward fasting level at three hours.

A group of larger premature infants, weighing more than 1,800 grams and between 24 and 48 hours of age, were given 0.5 Gm. of glucose per kilogram of body weight intravenously, and these curves compared with those obtained later in the neonatal period. These results are shown in Fig. 4 and Table III. Both sets of curves are again within normal limits, reaching the fasting level between sixty and ninety minutes, falling into a zone of

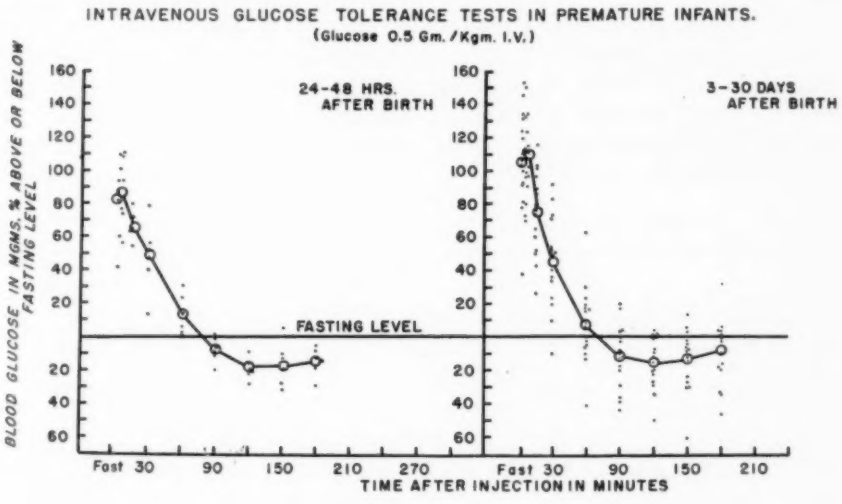


Fig. 4.

TABLE III. INTRAVENOUS GLUCOSE TOLERANCE TESTS IN PREMATURE INFANTS WEIGHING 1,800 GRAMS OR OVER (0.5 GM. GLUCOSE PER KILOGRAM INTRAVENOUSLY)

AGE	NO. OF CASES	FASTING LEVEL	PEAK RISE IN BLOOD GLUCOSE	TIME TO RETURN TO FASTING LEVEL	SUGAR LOSS IN URINE
24-48 hr.	6	42 ± 9	91 ± 18	All between 60-90 min.	0-1+
3-30 da.	16	56 ± 14	119 ± 20	30 min. to 2 hr. Majority: 60 to 120 min.	0-1+

deeper hypoglycemia followed by a return toward the fasting level at three hours.

In sixteen of these newborn and premature infants, urine specimens were obtained before and after the injection of glucose. In all cases in which the maximal blood sugar level was above 190 mg. per 100 c.c., glycosuria was present, and in none in whom the maximal blood sugar was below 134 mg.

According to Forsham and Thorn[9] a study of change in serum inorganic phosphorus levels during the glucose tolerance test is of value in determining the fate of injected glucose. These authors found a low fall in phosphorus (average 13 per cent) to be associated with the active entry of injected glucose largely into the liver, and a marked fall (average 37 per cent) in phosphorus largely into tissues other than liver, mainly skeletal muscle. They describe the combination of a normal or steep fall in glucose, together with a low fall in serum organic phosphorus as the reaction typical of a situation in which liver glycogen is depleted. In fourteen instances in which blood for inorganic phosphorus was obtained before and one to one and one-half hours after the injection of glucose, no significant change in phosphorus was noted. The majority of the serum inorganic phosphorus levels were unchanged, with only one falling as much as 20 per cent of the initial level after glucose injection.

BLOOD GLYCOGEN

Since newborn infants, on the basis of autopsy findings and the above epinephrine studies, may maintain a relative hypoglycemia in the face of large glycogen stores in the liver, the status of glycogen stores elsewhere in the body becomes of interest. In whole blood, glycogen is present, primarily or entirely in the mature polymorphonuclear cell.[6] Since it is not considered feasible to determine white cell glycogen in infants because of the large volume of blood entailed (12 c.c.) in this procedure, glycogen was determined in whole blood in duplicate 1 c.c. samples according to the method outlined by Wagner. The average glycogen content of normal human blood is given by Wagner as 5.5 mg. per 100 c.c. with a range of 1.2 to 16.2 mg.[6]

TABLE IV. BLOOD GLYCOGEN LEVELS IN NEWBORN INFANTS

PATIENT	NO. OF CASES	AGE		BLOOD GLYCOGEN LEVEL (MG./100 C.C.)		FASTING BLOOD SUGAR (MG./100 C.C.)	
		AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
Newborn infants	13	7 hr.	1-23 hr.	9	5-13	47	30-71
Older infants	4	7 da.	2-17 hr.	7	6-10	63	51-68
Adult controls	5	28 yr.	23-35 yr.	6	4-9	74	65-80

The values for blood glycogen obtained are shown in Table IV. It is seen that normal newborn infants, older infants, and adults all show values falling within the normal range as outlined by Wagner. Further evidence of the presence of glycogen in the polymorphonuclear cells of newborn infants was obtained by staining blood films, according to the method of Hotchkiss[10] which utilizes a periodic acid stain. Glycogen was readily dem-

onstrated in the polymorphonuclear cells by this method.

Therefore, it appears that the hypoglycemia of newborn infants occurs in the presence of a normal quantity of glycogen in the liver and in the polymorphonuclear leukocytes.

After delivery, the blood sugar of the infant falls from an initial level slightly below that of the maternal blood to its lowest value between four and eight hours after birth. Over the ensuing week the fasting level shows a gradual rise.[11] It seemed of interest

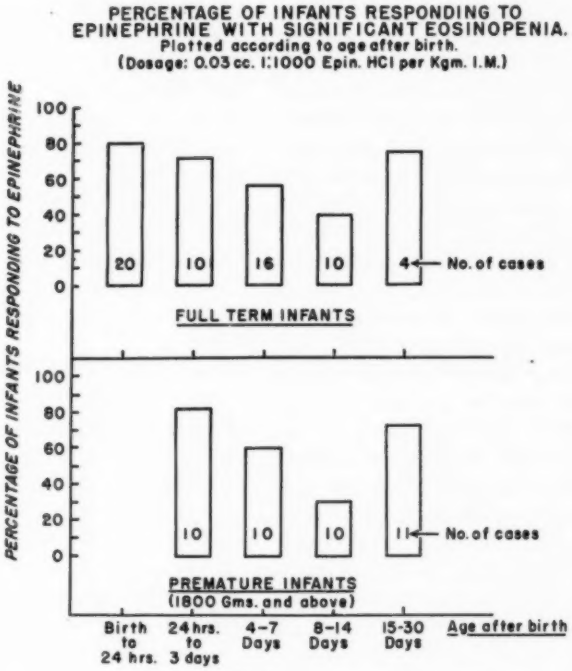


Fig. 5.

THE RELATION OF NEONATAL HYPOGLYCEMIA TO ADRENOCORTICAL FUNCTION

It has been suggested that a possible explanation for neonatal hypoglycemia might be found in a hypofunctioning of either the anterior pituitary gland or the adrenal cortex or perhaps a combination of both. The adrenal cortex is particularly interesting to consider in view of the rapid involution of the fetal cortex and gradual evolution of the true cortex after birth.

to follow the level of circulating eosinophils over the early hours after delivery in order to find if any consistent pattern existed which might be related to the immediate postnatal fall in blood sugar.

In the first twelve hours of life, fifteen newborn infants (including two premature infants weighing 2,180 and 1,984 grams) were subjected to repeated eosinophil counts at two- to three-hour intervals, with no exogenous stimulus other than that of the

pinprick. In the total group of fifteen, the eosinophil level of five remained essentially unchanged; in two, the number rose (20 per cent and 70 per cent); in eight, the number fell (four: 40 per cent to 90 per cent, and four: 20 per cent to 40 per cent). In five infants the blood glucose levels were followed along with the circulating eosinophils. All five showed a drop in blood glucose within eight hours as reported by Norval and associates,[11] but there was no consistent relation of glucose level to eosinophil level. In summary, 53 per cent of newborn infants showed a fall in circulating eosinophils within the first twelve hours after birth, a result suggesting that these infants were responding to the stress of immediate postnatal life. However, if the adrenal cortex were inactive, one would expect the eosinophil count to rise after delivery. It might be expected that if blood sugar level and eosinophil level were related to a hypofunctioning adrenal cortex, the direction of change in one would lead to an opposite change in the other. No such relationship was demonstrable here.

The response of circulating eosinophils to epinephrine injection was studied in a series of full-term infants and in premature infants weighing over 1,800 grams. The results obtained are shown in Fig. 5. In both groups, the eosinopenic response is essentially similar, varying with age after birth. The percentage of infants responding to epinephrine injection (0.03 c.c. per kilogram intramuscularly), with an eosinopenia of 39 per cent or higher, is greater in the first week of life than during the second, and increases again during the third week of life. During the second week of life both groups show a relative refractoriness to the eosinopenic effect of epinephrine while responding readily to the glycemic effect of the same drug (Fig. 1). It is these results which suggest that the glycemic and eosinopenic effects of epinephrine involve different physiologic pathways. The role of epinephrine in activation of the pituitary-adrenal axis is at present controversial,[12] so that it cannot be stated with any certainty that the anterior pituitary is relatively refractory to epinephrine during the second week of life in newborn infants, although it is conceivable that a refractory state might follow the cessation of flow of maternal hormones to the newborn infant.

DISCUSSION

The finding in the newborn infant of a slow response to the glycogenolytic action of epinephrine, together with a normal response to intravenously administered glucose, suggests that the breakdown of glycogen may be retarded in early life, while the uptake of glucose is normal. The physiologic hypoglycemia of early life occurs during a period when epinephrine injection will bring about a temporary rise in blood sugar, and when blood glycogen levels are within normal adult levels.

The pattern of circulating eosinophils after birth, and the eosinopenic response to epinephrine in newborn subjects, as well as the ability of the young infant to excrete glucocorticoids as shown by Venning and co-workers,[13] does not support a causal relationship between adrenal cortical insufficiency and neonatal hypoglycemia.

Perhaps these findings may be most easily explained by assuming a shift

in the direction of enzyme action in the first days of life. In utero, the infant is maintained in what might be considered a constant temperature water bath, and stores nutritional elements brought to it by the placental circulation. The infant has little need to break down stored carbohydrate for energy. It is known that glycogen is stored in increasing amounts as the fetus approaches term,[2] and it is possible that glycogen storage may occur under the influence of maternal and placental hormones, possibly progesterone, corticosteroids of placental origin, and an unknown growth-stimulating factor. After birth, the situation is changed drastically, and the infant is required to produce energy to maintain body heat. With separation of infant and placenta, the influence of maternal hormones is lessened, and the shift from an economy primarily concerned with storage to one concerned with energy production takes place. Potter, in his enzyme studies on the livers of newborn rats, has demonstrated an increase in biocatalytic concentration and a rapid development of an increased capacity for energy mobilization in late embryonic and early postnatal life.

If the period of hypoglycemia were related to pituitary or adrenal insufficiency, the infant could be expected to be refractory to epinephrine or ACTH administration at the time when the hypoglycemia is most severe, i.e., during the first few days of life. This has not been found experimentally.

CONCLUSIONS

1. Premature infants respond to epinephrine injection with a rise in blood glucose, as do full-term infants. In the first days of life, the increase in blood glucose is less and the rise less rapid than the rise at the end of the first week of life.

2. When the dosage of epinephrine is increased in full-term infants, the degree of glycemic response is increased.

3. The intravenous glucose tolerance curves of both premature and full-term infants are essentially within normal limits. Both groups demonstrate an ability to recover from the low levels reached in the rescending limb of the curve.

4. Serum inorganic phosphorus in the blood of newborn infants does not fall appreciably after the intravenous administration of glucose.

5. Blood glycogen levels in the newborn period are within the normal adult range.

6. Within the limits of this study, no relation could be demonstrated between the eosinopenic and glycemic response of the newborn infant to epinephrine injection.

7. Theories of the origin of the phenomenon of neonatal hypoglycemia are discussed. A suggestion is proposed that the period of neonatal hypoglycemia may represent a transition period between a fetal metabolism concerned primarily with storage to an extrauterine metabolism necessitating the need to produce energy by carbohydrate breakdown. The transition may be conditioned by the separation of the infant from the flow of maternal hormones.

The author wishes to express her appreciation to Dr. Russell J. Blattner, Professor and Chairman of the Department of Pediatrics, Baylor University College of Medicine, for his encouragement and guidance during the course of this study, and to Dr. J. H. Gast,

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CHRONIC URINARY TRACT INFECTION IN A FEMALE CHILD

Recovery After Vaginal Estrogen Therapy

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URINARY tract infections are commonly implicated as the cause of obscure febrile diseases in childhood. These infections are always a cause for concern because of the frequent association of infection with congenital anomalies of the urinary tract. However, the female child is predisposed to retrograde seeding of bacteria into the urinary tract by the close proximity of the urethra to the moist, contaminated anovaginal region.

Perhaps infection should be considered more commonly in the management of enuresis. Symptomatic evidence of urinary tract infection does not consistently include fever and may be manifested by disturbances of behavior and appetite, urgency or frequency of urination singly or in association with more evident signs of infection.

Campbell[1] has repeatedly emphasized that the child with persistent enuresis, after three to four months of intensive medical management, deserves urologic study. In over 1,500 patients with persistent enuresis, he found two-thirds of them to have urinary pathology. Erb and Summerfeldt[2] reported an incidence of 4.4 per cent of congenital anomalies of the urinary tract in 1,148 autopsies. Of those with anomalies, 43 per cent had evidence of inflammatory disease in the urinary tract. Many of the patients were not suspected of having inflammatory disease, as they had negative urinalyses.

Infection of the lower urinary tract is also found without congenital anomaly or obstructive phenomenon being present. Benson and Weinstock,[3] in reviewing the results of the therapy of gonorrheal vaginitis in the preantibiotic days, reported that 439 of 1,232 patients with gonorrheal vaginitis had urethritis as a complication. They suggested that many of the reported cases were caused by organisms other than the gonococcus, as the bacteriologic studies were not always complete. Campbell[4] noted that urethrotrigonitis was the most common organic cause of enuresis. Thirteen of sixty-six patients having urethrotrigonitis had an associated vaginitis.

Hanley[5] described bladder symptoms seen in the female and stated that local irritation was the chief cause. The effect of cystitis was said to be spasm or contraction of the muscular wall of the bladder, so that bladder capacity is reduced. Urethral spasm when present may produce a constant desire to pass urine.

CASE REPORT

J. W., 5-year-old white female, was the second child of three in the family. The course of infancy was uncomplicated. The parents first be-

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came concerned because the child seemed unable to control urination at the usual age for toilet training.

At the age of 2 years a urinalysis revealed "mucus, pus, and red cells." A brief course of sulfonamide therapy appeared to control the diurnal enuresis but recurrence of the symptoms occurred three weeks after treatment.

Repeated urinalyses were negative after the first examination at 2 years. However, despite absence of abnormal urine findings the patient continued to show frequency, diurnal enuresis, and occasional low-grade fever. Many courses of treatment, including various sulfa preparations, streptomycin, aureomycin, penicillin, and mandelic acid, were used. Each time there was temporary improvement. Exacerbations, numbering five to six per year, occurred after each course. Cystoscopies and retrograde urography at ages 3 and 3½ years were twice negative.

Physical examination revealed a very well-adjusted and cooperative patient who was anxious to be relieved of her condition. Developmental status was above average. She was afebrile and well nourished. Her height was 40 inches, weight 40 pounds, blood pressure 75/30. There was no evidence of infection in sites other than the genitourinary tract. The urethral meatus was of normal size and appearance but the vulva and intererural folds were moist and red, with mild maceration. The introitus appeared excessively moist and red. No foreign body of the vagina could be palpated by rectal examination.

The hemogram was: hemoglobin 10 Gm. per cent, white blood count 10,800 per cubic millimeter. A catheterized urine specimen was free of albumin but a few gram-negative bacilli and 1 WBC/hpf were seen on microscopic examination. Culture was positive for *Eschericia coli*. A culture from the vagina also showed *E. coli* organisms. An intravenous pyelogram was normal.

The urethral sphincter was slightly relaxed and cystoscopy was easily done.* Intensive contracture and smooth muscle spasm of the bladder was evident and heavy edematous folds of mucosa stood out. The mucosa was red and injected, with shreds of shaggy exudate attached near the ureteral orifices. Indigo carmine dye was injected intravenously and a ureteral catheter used to probe all folds in the bladder and vagina that might obscure an ectopic ureteral orifice. The results were negative. A urine specimen obtained from the right ureter was positive for *E. coli* on culture. Retrograde pyelograms again revealed no pathology.

Treatment was begun with oral Gantrisin 4 Gm. daily in four divided doses, and warm sitz baths. After one week of therapy the patient had had only two episodes of enuresis. The urgency and malodorous vaginal discharge were absent. A white blood count was 5,000 per cubic millimeter. A catheterized urine specimen was negative to examination and culture. Improvement had occurred in spite of the fact that in vitro antibiotic sensitivities of the previously isolated *E. coli* organism were as follows:

Drug	*Inhibitory Level* (μg %)
Terramycin	2.81
Streptomycin	3.5
Chloromycetin	5.7
Aureomycin	11.3
Gantrisin, Sulfadiazine	No inhibition

A recurrence of symptoms which appeared to be related to the onset of epidemic parotitis occurred near the end of the first month of treatment with Gantrisin. Treatment was not changed or discontinued and the symptoms subsided as the parotitis improved. Gantrisin therapy was discontinued after two months and the patient temporarily remained symptom-free.

*All urological procedures were performed by Dr. James Headstream, Associate Professor of Surgery and Head of the Division of Urology.

One month after cessation of treatment there was a return of symptoms. Cultures of the urine were again positive for *E. coli,* and for *Staphylococcus albus.* Terramycin, 1 Gm. in four divided doses daily, was given for two weeks and quickly relieved the symptoms. The benefit was, however, of short duration and a culture of the urine taken shortly thereafter revealed a Proteus bacillus.

Cystoscopy was repeated and the bladder found to be entirely free of the previously described picture of chronic inflammatory disease. Attention was again turned to the vagina as there appeared to be a return of the vaginal discharge with each exacerbation of symptoms. A strict hygienic program was instituted, using warm dilute acetic acid sitz baths, careful cleansing of the anus after defecation, and special treatment of the undergarments with antiseptics during laundry. Temporary cessation of symptoms again occurred but in three months symptoms recurred and *E. coli* organisms were again cultured from the urine. Courses of Gantrisin and Prohydrion therapy seemed temporarily helpful.

Thirteen months after the patient's first visit a sixth exacerbation occurred. At this time the cervix and vagina appeared chronically infected. Smears of the seropurulent vaginal discharge showed many pus cells and large numbers of gram-positive cocci. Culture for Neisseria organisms was negative. The epithelial cells present were the normal unestrogenized cells of the vagina of a child.

The usual antibiotic and hygienic measures have been ineffective in maintaining persistent relief of infection in both the urinary tract and vagina. Since, in the preantibiotic days, estrogenation of the vaginal tract had been successful in the treatment of vaginitis it was decided to administer diethylstilbestrol locally.

One suppository (0.1 mg.) was inserted deep into the vagina each night before bedtime for one week. By the end of the week smears taken of the vaginal discharge from deep in the vagina showed good estrogen effect. The mucosal cells were flat, folded, cornified squamous cells of the adult type. Few pus cells were found. Simultaneously there were an abrupt cessation of urinary symptoms, a disappearance of the foul vaginal discharge, and a general elevation of mood of the patient. The estrogen effect was maintained by insertion of a suppository on alternate nights for five more weeks.

At the time of this writing, one year after the course of diethylstilbestrol was started, the patient is still completely symptom-free and occasional "clean-catch" urine cultures have all been negative for bacteria.

DISCUSSION

The sudden disappearance of diurnal enuresis, malaise, frequency and urgency with onset of the first evidences of estrogenation of the vaginal epithelium was no different than that following the previous types of therapy. The remarkable result in this case was the effect obtained by inducing the development of an adult type vaginal epithelium of freeing the urogenital tract of a smoldering, low-grade infection.

A review of the literature revealed that Lewis, in 1933, first used locally applied estrogens for the relief of gonorrheal vaginitis in children. Estrogenation reached wide acceptance for this purpose prior to the advent of antibiotics. Te Linde[6] reported in 1938 that he had treated 159 cases of gonorrheal vaginitis with Amniotin locally to the vagina. All patients were cured of their condition. Two prime factors appeared to work in ridding the vaginal tract of infection: (1) the reduction of the vaginal pH,

and (2) stimulation of growth and development of a vaginal mucosa similar to that of the adult. The gonococcus is inhibited in growth by a pH below 6.2. Estrogen therapy was successful in dropping vaginal pH to 4.8 to 6. The average after-treatment pH obtained was 5, compared to pH 7.5 before treatment. The average time for the development of estrogen effect was two weeks. No significant amount of absorption was thought to occur from the vagina. No complications were observed.

All reported cases that were reviewed were in patients treated for gonorrheal infection by use of injected or locally applied estrogen. In no case was there reference to the effect of estrogen therapy on urinary infection not associated with gonorrheal vaginitis.

The case herein described suggests that the use of estrogenation might be expanded to the treatment of intractable vaginal infections of other bacterial cause, with or without associated urinary symptoms.

SUMMARY

1. The importance of investigating the urogenital tract in intractable enuresis in the child is re-emphasized.

2. A case is presented which exhibited the picture of intractable enuresis thought to be related to a chronic low-grade vaginitis not caused by the gonococcus.

3. Successful use of local estrogen treatment to the vagina and consequent relief of the urinary symptoms is described.

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A STUDY OF FORTY CASES OF RINGWORM OF THE SCALP

In Hagerstown Schools, 1950 and 1951, Washington County, Maryland

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IN THE fall of 1950 patches suspicious of tinea capitis were observed in several boys in one of the Hagerstown schools. The children were referred to the school's public health nurse for examination under the Wood's lamp. The diagnosis of ringworm was confirmed and the heads of all classmates of the infected children were then examined. It was apparent that an epidemic was developing and immediate steps were taken to meet the exigency for control and prevention of further spreading of the disease.

In 1944 an outbreak of ringworm had occurred in this same community.[1] At that time consultants from the Dermatoses Section of the Industrial Hygiene Division of the Public Health Service were delegated to establish a program to combat this situation. The older methods of isolation or exclusion of infected children from school, and treatment by x-ray epilation, were not followed on the premise that spread of infection would continue outside the school grounds. Moreover, there were not sufficient x-ray units and technicians available to carry out treatment in the large number of children affected over a wide area. In addition, careless disposal of x-ray-epilated hairs would tend to spread the infection. The recommendation was made that the children continue to attend classes and that a topical treatment program be undertaken during school hours. In view of the previous successful experience with such a regimen, it was decided to institute similar measures to meet the present emergency.

In the hope of curtailing the spread of infection the nursing staff of the Health Department, school principals, and all physicians in the area were alerted to watch for the disease. To enlist cooperation in the treatment and control program, the newspapers published warnings and general information for public education on preventive measures. The Health Department sanitarians were consulted and cooperated in visiting key barbershops and the local barber school in Hagerstown to educate the personnel in methods of checking this important source of spread of the disease. All of the barbershops attended by the infected children were visited and hairs from clippers used in these shops were examined under the Wood's lamp.

A ringworm clinic was established in one of the schools and clinic sessions were held weekly until all of the elementary grade children in the

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area had been examined. When a case was referred from a junior high school grade, all pupils in the class involved were examined. As a result of the general survey most of the forty cases to be reported below were detected in the fall and early winter of the 1950-1951 school term. All cases except the one in junior high school (aged 14 years) were in the elementary grades.

In this series eight cases were found in white boys from four different schools, and twenty-seven in Negro boys and five in Negro girls, all from the same school. The first case developed in the summer of 1950; during the fall and winter of that year twenty-six cases occurred; in the spring of 1951, four developed; in the summer, three; and in the fall, six. There were no cases detected in the first part of 1952. All forty cases were Wood's light positive, and cultures performed in twenty-eight were positive for *Microsporum audouini*.

TREATMENT PROGRAM

Medicaments.—When the clinic was first established it was planned to treat alternate cases with 5 per cent salicylanilide ointment and with 5 per cent Asterol Dihydrochloride in the form of ointment and tincture.* Manual epilation was also to be employed. Since the initial results with the Asterol preparations showed a rather rapid elimination of fluorescent hairs, rendering the cases less infectious, the study was soon limited in the clinic program to treatment with the Asterol preparations. However, ten patients in the series were treated with other measures usually provided by private physicians, as recorded in Table I.

Instructions for Home Treatment.—The parents of infected children were given the following instructions: Shave or clip the hair short every seven to ten days. Shampoo the head every other day. Spray the tincture over the entire head each morning and rub it in gently with a toothbrush moistened with the tincture. Apply the ointment with the toothbrush in the same manner at bedtime. Keep the child's head covered day and night with a tight-fitting cotton skull cap.* Boil the cap every two days. Use Asterol Tincture to spray frequently the child's cap and parts of the clothing which might be contaminated with infected hairs.

Clinic Procedure and Criterion for Cure.—For each child a record form was provided to show the extent of the lesions and for entry of the patient's progress. An outline of the skull was included on the form and the infected areas were defined by using a solid line circle to show a solid area of ringworm infection, dots to indicate a few scattered fluorescent hairs, and a broken line circle to show any extension of the initial lesion. The infected areas were then labelled alphabetically and the results of treatment in each area recorded separately. Fig. 1 illustrates a completed record form for one patient in the series.

The parents were urged to attend the semimonthly examinations in the clinic supervised by the school nurse and the monthly examinations by the pediatric consultant. The parents were also asked to bring along pre-

*Asterol Dihydrochloride Tincture and Ointment were furnished by Hoffmann-La-Roche Inc., Nutley, N. J.

*Cotton cap material was supplied by local Red Cross Chapter.

WASHINGTON COUNTY, MARYLAND

DEPARTMENT OF EDUCATION — DEPARTMENT OF HEALTH

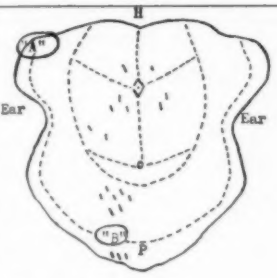
Name --------, Terry — Grade 1st

School Winter Street — Public Health Nurse F. Grove

Mother can be contacted at ------
Phone ------

RINGWORM RECORD
Checked every 2 weeks in School Clinic

Lesions



Types of Treatment

Asterol
Tincture)
Ointment) 4/9/51

*Mother given ringworm direction forms.

Culture--
Positive for microsporum audouini.

No reaction. At Health Dept. (((

*This case was well handled by parents.

Date	Progress	
4/6/51	Large area of what appears to be	Mother present
	an old lesion of active ringworm	
	at "A" with scattered isolated bright	
	green hairs over head. Many epilated	
	today.	
4/26/51	Hairs are now gray over original area	
	"A." A couple of grey ones in front	
	near midline and a few appeared at "B"	
	near neckline. These were epilated.	
	Head cleanly shaved. Mother carrying	
	out directions well. No reaction.	
5/11/51	No green hairs seen today. All gray.	Aunt present
	Head shaved nicely. Continue treat-	
	ment. Discard present covering and	
	wear the stockingette cap.	
6/16/51	Negative. Continue treatment.	Aunt present
7/12/51	Negative. Continue treatment.	Aunt present
8/17/51	Negative. Discontinue treatment.	
	Let hair grow.	
9/9/51	Negative.	
5/28/52	Negative	

Fig. 1.

school siblings for examination. When a parent failed to accompany the child on the examination day, the nurse would visit the child's home in an effort to enlist better cooperation.

Medication was generally continued for six weeks after the first negative examination under the Wood's lamp.

The patient was considered cured if the routine examinations remained negative for two months after therapy was discontinued.

RESULTS OF TREATMENT

The results of the various treatment regimens employed are recorded in Table I. Thirty-three patients were cured,* one was lost from observation, and six were failures.

*The thirty-three patients were re-examined in June, 1952, and no relapses were found at that time.

Cures.—Of the twenty-seven patients treated with Asterol Ointment and Tincture alone, seventeen showed no evidence of green fluorescent hairs after one month of treatment, six after two months, and three after three months. One child who had absence of green fluorescence in two months had a relapse because of neglect of treatment during the two summer vacation months. On reinstitution of therapy there was subsidence of the infection in two months.

The time required for cure was expressed as the interval between initiation of Asterol therapy and first Wood's light negativity although, as stated, treatment was continued beyond this point.

On the Asterol regimen cure was obtained in one patient in one month, in three in two months, in nine in three months, in five in four months, and in two in five months. Six months were required for cure in two patients and nine months in one patient. In these latter three cases treatment had been neglected during the summer months and relapses had occurred. One patient moved from the area and could not be declared cured by our criteria although the infection had subsided in this patient within the first month of treatment.

Asterol and roentgen-ray epilation were used in two patients, one being considered cured after four months and the other after five months of

TABLE I. EFFECTS OF TREATMENT OF TINEA CAPITIS IN FORTY PATIENTS

METHOD OF TREATMENT	NO. CASES	TIME REQUIRED FOR FIRST ABSENCE OF GREEN FLUORESCENCE AND FOR CURE			FAILURES	LOCALIZED REACTIONS	LOST FROM OBSERVATION
		TIME (MONTHS)	FIRST ABSENCE OF GREEN FLUORESCENCE NO. CASES	CURE NO. CASES			
Asterol Ointment and Asterol Tincture	27	1	17	1	3	2 mild	1
		2	6	3		1 moderate	
		3	3	9		1 severe	
		4		5			
		5		2			
		6	1*	2*			
		9		1*			
Asterol + x-ray	2	4		1			
		5		1			
Salicylanilide + Asterol + x-ray + Asterol	1	18	1	1			
Salicylanilide ointment	2	3	1	1	1		
		4					
Salicylanilide (1 month only, manual epilation)	1	9		1			
X-ray	1	4		1			
Manual epilation only	1	6		1			
Walnut juice + x-ray	1	?		1		1 severe	
Unknown + x-ray	2	2	1	1			
		3	1		1		
Unknown	2	1	1	1		1 severe	
		2			1		
Totals	40		31	33	6	6	1

*Neglect of treatment during summer months caused relapse; evaluation of results estimated from time of intial lesion.

treatment. Another patient was treated with salicylanilide ointment, then Asterol, followed by x-ray epilation, and subsequently by Asterol. Eighteen months were required before cure was effected. Salicylanilide ointment alone was used in two patients. This treatment resulted in cure in one patient in four months and the other patient failed to respond. In one patient salicylanilide ointment was applied for one month and then manual epilation was used as the only measure of treatment. Nine months were required for cure in this patient. The results in the above patients and in the remaining seven patients treated by other measures are shown in Table I.

Failures.—Failure to respond to treatment, or the length of time required to effect a cure, is influenced not only by the severity of the infection, but more significantly by the degree of parent cooperation. The six cases failing to respond were those in whom parental neglect was the prime factor. In all of these cases the public health nurse made frequent visits to the patients' homes in an attempt to overcome the indifference of the parents. Despite these intensive efforts, the medication was either applied irregularly or inadequately, or there was complete neglect.

Reactions.—As recorded in Table I reactions occurred in six patients. The four reactions following Asterol therapy occurred in children who had not received any previous medication. These reactions were characterized by erythema and pustule formation usually around the infected areas, associated with an "id" type reaction of small ringlike formations. In two patients who had mild reactions of this nature treatment was continued. In one of these the reaction disappeared in one week, and activity of the ringworm infection was controlled in two weeks. The parents of the other child were warned to apply the ointment and tincture more gently and to exert caution in shaving the child's head. Within twenty days the reaction subsided. Spreading of the disease was controlled in two months and cure was attained in four months from the initiation of treatment. In the third patient, with a moderate reaction, Asterol Tincture was continued but the ointment and shaving were discontinued because the lesions had become very raised, thickened, and tender. One month later the areas of reaction were sore and red but nonpurulent. Wood's light negativity was obtained three weeks later and both tincture and ointment were applied for another six weeks without untoward effect. In the fourth child a severe reaction developed after three months of therapy. This was two weeks after Wood's light negativity had been attained. The ointment was discontinued and only the tincture applied. The reaction became more severe and three weeks later the patient was hospitalized because of fever and listlessness. Thick crusts formed after the secondary infection had subsided following application of wet soaks and administration of penicillin intramuscularly. Roentgen-ray epilation was performed in the hospital, but a month later two active lesions were discovered. These areas were epilated manually and no further treatment was given. Two weeks later a negative examination was obtained. In the next months the

hair regrew and there were no scars or evidence of ringworm infection.

In one Negro boy application for about one week of a home remedy of walnut juice produced an extremely severe widespread secondary reaction and infection necessitating hospitalization. X-ray epilation was then carried out at the hospital. In another boy a severe reaction requiring hospitalization occurred following use of an unknown ointment obtained from the family physician.

DISCUSSION

Asterol Dihydrochloride provided a practical means of treatment of tinea capitis due to *M. audouini* in the 1950-1951 Hagerstown epidemic. The medication could be easily applied by the parents, and where good cooperation was obtained the infection was brought under control quite rapidly.

After trial in the early cases manual epilation was utilized only on those cases in which there were very small lesions or single infected hairs. It was found too time consuming for the nurse to epilate the larger patches and experience in the first twelve cases did not indicate that healing was greatly facilitated with this technique. It did not seem advisable to request parents to undertake epilation in view of the possible careless disposal of infected hairs and the fact that this would be a tedious procedure further complicating the involved regimen of shampooing, clipping or shaving the hair, boiling of caps, and administration of the medication. Shaving, although it irritated the scalp somewhat, was a more effective measure than clipping, but in some cases there was considerable objection to exposing the scalp.

The results obtained with Asterol in the twenty-seven cases in which it was used as the sole medication compare favorably with those reported by several other investigators. Cures were obtained in eighteen patients, or 66 per cent, within four months. Stritzler and associates[2] reported that from six to twelve weeks were required for the first negative Wood's light examination in approximately two-thirds of their series of eighty-three patients treated with Asterol. Fifty patients, or 60 per cent, were cured in this series. Edelson and associates[3] found that the period of treatment required for first Wood's light negativity ranged from two to seventeen weeks, with an average of nine weeks. They treated seventy-two patients with Asterol and the incidence of success was 66.6 per cent. In a subsequent study of sixty-one patients these same workers reported[4] a cure rate of 68.9 per cent.

SUMMARY AND CONCLUSIONS

An epidemic of tinea capitis developed in the schools of Hagerstown, Maryland, during the fall of 1950. A program for treatment and prevention of spread of the disease was initiated by the Washington County Health Department.

During 1950 and 1951 forty cases were diagnosed as ringworm infections under Wood's light. Cultures in twenty-eight were positive for *M. audouini*.

Twenty-seven patients were treated with Asterol Dihydrochloride Tincture and Ointment alone, two with Asterol in combination with roentgen-ray epilation, one with Asterol, salicylanilide ointment, and roentgen-ray therapy, and the remaining ten by various measures. Treatment was

carried out in the patients' homes and semimonthly examinations were made in the school clinic.

In this series thirty-three patients were cured, there were six failures, and results in one patient could not be evaluated.

Response to therapy was significantly related to the degree of parental cooperation in carrying out the treatment regimen.

Six localized reactions to therapy occurred, four following Asterol therapy, two of which were mild, one moderate, and one severe. Two severe reactions occurred as a result of other measures.

Asterol Dihydrochloride Ointment and Tincture provided a most effective and practical medication for the cure of tinea capitis and for prevention of further spreading of the disease.

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CONGENITAL HYPERHIDROSIS

Therapy With Hydergine and Banthine

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DURING the last ten years an increasing number of case reports and descriptions of treatment of hyperhidrosis in adults have appeared in the medical literature. A few cases in children have been referred to in several of these articles, but detailed reports are very scarce. Because of the infrequency with which this is encountered and the difficulties attendant to successful therapy, the following report of a new therapeutic agent is offered.

CASE REPORT

The patient (D. C.) is a 9-year-old white girl who was apparently well until the age of 3 months when the parents first noticed excessive sweating of the hands and feet. This has continued constantly throughout her life and has been little effected by temperature changes, although it has been more severe during very hot weather and when she becomes emotionally upset. The wet hands have caused her considerable embarrassment and have interfered with her schoolwork. Trichophytosis of the feet has been very constant and extremely difficult to control.

Six months prior to her admission to Childrens Hospital, blanching of the fingers and toes was first noticed. This, too, has been constant and has been accompanied by decreased skin temperature of the involved areas. There have been no subjective complaints or decrease of function. During the year prior to admission she was treated with Banthine with only slight decrease in sweating. There was no significant associated past history. Her paternal uncle has had similar difficulty since childhood.

The significant physical findings on admission to the Childrens Hospital were limited to the extremities which revealed excessive sweating on both the volar and dorsal surfaces of the hands and feet. The hands and feet were cooler than the other parts of the body, and the distal portions of the fingers and toes were very pale with smooth, thin skin. The subcutaneous tissue was decreased so that the fingers appeared to be tapered at the ends. Routine laboratory studies were within normal limits. Special vascular studies revealed*:

Arterial Pulsation of Digits (cu. mm.)		
	R	*L*
Fingers	5.0	4.0
Toes	1.0	1.5
Following right tibial Novocain block		
Toes	5.0	1.0
Blood Flow of Digits (cu. mm./sec.)		
	R	*L*
Fingers	17.0	18.0
Toes	1.0	1.5
Following right tibial Novocain block		
Toes	19.0	2.0
Skin Temperature of Digits (° C.)		
	R	*L*
Fingers		35.5
Toes	28.0	27.0
Following right tibial Novocain block		
Fingers		26.0
Toes	36.0	28.0

Similar studies with the adrenolytic agent, Hydergine,† revealed the following:

From the Department of Pediatrics, Childrens Hospital and University of Southern California School of Medicine.

*These studies were done at the Cardiovascular Research Laboratory of the Good Samaritan Hospital by Dr. Travis Winsor.

†Generously supplied by Mr. H. Althouse, Sandoz Chemical Works, Inc., San Francisco, Calif.

Arterial Pulsation of Digits (cu. mm.)

	R
Toes	0.5
Following 2.6 mg. Hydergine (subc.)	
Toes	4.0

Blood Flow of Digits (cu. mm./sec.)

	R
Toes	2.0
Following 2.6 mg. Hydergine (subc.)	
Toes	11.0

Skin Temperature of Digits (° C.)

	R	*L*
Fingers		26.0
Toes	26.0	26.0
Following 2.6 mg. Hydergine (subc.)		
Fingers		34.5
Toes	33.5	33.5

Above figures demonstrate symmetrical, decreased vascular pulsation and blood flow in fingers and toes. Nerve block achieved vasodilatation as evidenced by flushing and increase of pulsation, blood flow, and skin temperature. Sweating of the right foot was completely abolished by the block. Studies with the adrenolytic Hydergine demonstrated similar simultaneous changes in all four extremities. Banthine was shown to moderately decrease, but not abolish, sweating of the hands and feet.

The effect of psychic stimulation was striking with apprehension resulting in decreased skin temperature and profuse sweating of hands and feet.

At discharge she was placed on oral Hydergine, 1 Gm. every three hours during the day, and Banthine, 50 mg. three times daily. During the next nine months she experienced marked relief. In spite of excessive hot weather, her hands and feet remained almost completely dry with skin pallor replaced by a natural pink color.

DISCUSSION

The sweat glands receive their innervation from centers in the hypothalamus and possibly from other centers at a higher level. From these centers sympathetic pathways course downward through the intermediolateral columns of the cord and pass out in a segmental manner to the ganglionated chains as white rami. Postganglionic fibers extend from the ganglion to the peripheral nerves as gray rami to innervate the blood vessels and sweat glands.

According to Haimovici,[1] it has long been known that sweat glands are under control of the sympathetic nervous system but respond to parasympathethic drugs. He demonstrated by intradermal injection of both epinephrine and acetylcholine, or Mecholyl, into the same point that the secretory activity of the sweat glands was stimulated by cholinergic and adrenergic drugs. He concluded that as these agents exert a synergistic sudomotor action, and since sweating in man can be produced by adrenergic agents and inhibited by an adrenergic blocking agent, that in addition to the known cholinergic fibers supplying the sweat glands, there is also an adrenergic component in the nervous mechanism of sweating in man.

The usual stimulus to sweat gland secretion is a rise in the blood temperature which exerts its effect in two ways: directly on the nervous centers and reflexly by stimulation of the heat receptors in the skin. A rise in the temperature of the sweat centers alone will produce sweat although the region involved itself remains cool. Sweat response to a rise in temperature is abolished by sectioning the nerves to a part, and is therefore not due to direct stimulation of the glands. Experimentally, sweating can be produced by stimulation of the hypothalamus. There are also spinal centers for sweating since transection of the cord is followed by reflex sweating in the part of the body below the lesion. Sweating is not dependent upon circulation since it occurs after vascular occlusion.[2]

Although usually associated with cutaneous vasodilatation, sweating may occur with constricted vessels—so-called cold sweat. This type of sweating usually follows psychic stimuli such as nervousness, fatigue, fear, and mental work and occurs mainly on the palms, soles, and forehead.

In certain types of abnormal stimulation or from increased sensitivity of the sympathetics, some of the normal reactions are so exaggerated that a distinct pathological entity is produced, i.e., hyperhidrosis.

Veal and Shadid[3] reported sixty-one cases of hyperhidrosis occurring mainly in adults. One case was in a child 8 months of age. Excessive sweating occurred in these patients in which actual beads of sweat dropped from the forehead, palms, and soles. In these patients, vasodilatation, tachycardia, vasomotor instability, emotional imbalance, and inner tenseness were accompanying factors.

Hyperhidrosis is usually a functional disease, but certain pathological entities may be associated with it. If the exciting stimulation arises from levels below the brain, it is usually organic in nature. Trauma or inflammatory lesions of the spinal cord, peripheral nerves, nor blood vessels may provide the necessary stimulation. Poliomyelitis, peripheral neuritis, neuromas of the peripheral nerve, or frostbite may also produce hyperhidrosis, and it has also been reported to occur with brain tumors or traumatic or inflammatory diseases of the brain. When no organic cause can be shown to be present, it is designated as primary hyperhidrosis. This type usually begins early in life and there is often a family history of the disease. Early symptoms may be very mild until there is some aggravation such as fatigue, anxiety, pain, or mental anguish. Sweating is usually intermittent with patients responding to heat and exercise by unusually profuse sweating.

Until recent development of satisfactory sympatholytic agents, surgical sympathectomy was the only effective treatment. A number of drugs have been used, such as Dibenamine, Benzodioxane, Regitine, and other experimental products. Hydergine, used in our patient, is a mixture of dehydrogenated ergot alkaloids with a sympatholytic effect, blocking sympathetics at the neuroeffector junction.[4] It also has a central effect. The therapeutic dose sometimes closely approximates the toxic dose producing headache, nausea, vomiting, lethargy, irritability, and electroencephalographic changes. Manifestations of its effect may be marked hypotension, fainting, and occasionally abdominal cramps. As a result of its action, dilatation of the arterioles and venules results, more marked in the venules than the arterioles. There is a decrease in blood pressure, and increase in the venous pressure, and a decrease in the size of the heart. The cardiac output is decreased due to pooling of the blood on the venous side of the circulation.[5] Banthine has also been used with variable success in the treatment of hyperhidrosis due to its effect of blocking the parasympathetics.[6]

The differing modes of action of these two drugs suggested their simultaneous use in our patient, which has apparently been of more value than when either was used alone. For several months her hands and feet have been dry, warm, and pink in color.

She has, however, been forced to continue medication at three-hour intervals during the day, which proves to be a most irritating chore. As this will have to be continued indefinitely, the question of surgery may be seriously considered in the future. It is also known that the effects of the sympatholytic drugs may gradually lessen when given over a prolonged period of time. Should this occur, larger dosage would be indicated or perhaps shift to a different preparation.

Surgical management is worthy of future consideration as one can sympathectomize one or all four extremities with permanent effect. There is no significant recurrence of sweating after appropriate sympathectomy, and the chance of vasoconstrictor effects due to Adrenalin sensitivity is exceedingly low. Therefore, sympathectomy is highly satisfactory and carries a relatively low risk.

One might suppose sympathectomy of four extremities would cause oversweating of the trunk. This is not true because sweating of the trunk is not set off by emotion to any important degree. Persons who have had quadrilateral sympathectomy perspire excessively on the trunk when exposed to hot environment, but not after emotional stimulation.[7] Hence, these patients should avoid an unusually hot environment whenever possible.

SUMMARY

Congenital hyperhidrosis in a child is a rarely reported condition. This case report is presented with a discussion of etiology and treatment. It is possible that discovery of other new drugs which have an adrenolytic effect may obviate the need for sympathectomy. A combination of Hydergine and Banthine has given extremely satisfactory results in this patient.

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CHOREA MINOR

Preliminary Report on Six Patients Treated With Combined ACTH and Cortisone

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THE therapy for chorea has been a subject for varied reports with new panaceas being offered and discarded just as often.

One of the newer treatments that has been proposed and now scrutinized is the use of ACTH and cortisone. There has been no definite agreement since some[1-6] report favorable results while others[5-8] report no effect at all. Some of the former proponents have claimed that the reason for the others' failure was inadequate dosage. Moreover, some of the workers with these hormones have cautioned that the use of these products might suppress the activity of the adrenal, or the pituitary.

With both of these objections in mind, it was felt that perhaps they could be circumvented by utilization of a combination of ACTH and cortisone. By this combination, it was hoped that the same effect could be obtained by one-half or one-third of each in combination as compared to their individual administration. If this were true, then smaller doses of each might also cause less suppression of glandular activity.

With this as the objective, ACTH and cortisone were used simultaneously in various ratios ranging from 1:1 to 1:3 and given every six hours. This was tried in six cases of chorea, summaries of which follow:

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CASE REPORTS

Case 1.—M. S., a 7-year-old male, was admitted on July 23, 1953, with a history that three weeks prior to admission he began to manifest bizarre movements of the right wrist and right lower extremity. He also dragged his right foot when walking, tired easily, began to grimace, and his speech became slow and slurred. Shortly thereafter the left upper and lower extremities became involved. These movements were also noticed when he slept.

Prior to this illness he had a history of frequent respiratory infections including sore throats. The family history revealed that he had one sister who had chorea and rheumatic carditis, and his mother had rheumatic heart disease. His two brothers, however, were normal.

Upon physical examination, it was noted that he displayed facial grimaces, slow slurred speech, marked athetoid movements of both hands and feet, and marked weakness of the right upper and lower extremities. His coordination and muscle tone were particularly poor on the right. In walking, he dragged his right foot, leaned toward the right, and did not swing his right arm. He had hyperactive reflexes and bilateral hanging reflexes were obtained.

On July 26 he was started on ACTH and cortisone, 5 mg. of each every six hours. By the eighth day moonface became noticeable and choreiform movements were decreasing. Improvement continued, moonface did not progress, blood pressure and weight remained stable, and by August 18, the chorea had cleared completely and medication was stopped. The hanging reflex was gone, and the patient

was discharged on September 15 as asymptomatic.

CASE 2.—M. R., a 13-year-old Puerto Rican female, was admitted on July 28, 1952, with a history of a four-day illness with bizarre purposeless movements of all extremities and difficulty in talking, with the speech being muffled and slurred.

ity to coordinate body movements, and bilateral hanging reflexes were elicited. She also had a harsh blowing systolic murmur over the mitral region which was not transmitted.

On August 1 she was started on ACTH and cortisone, 5 mg. of each every six hours, but no improvement was noted in ten days, so the dose was

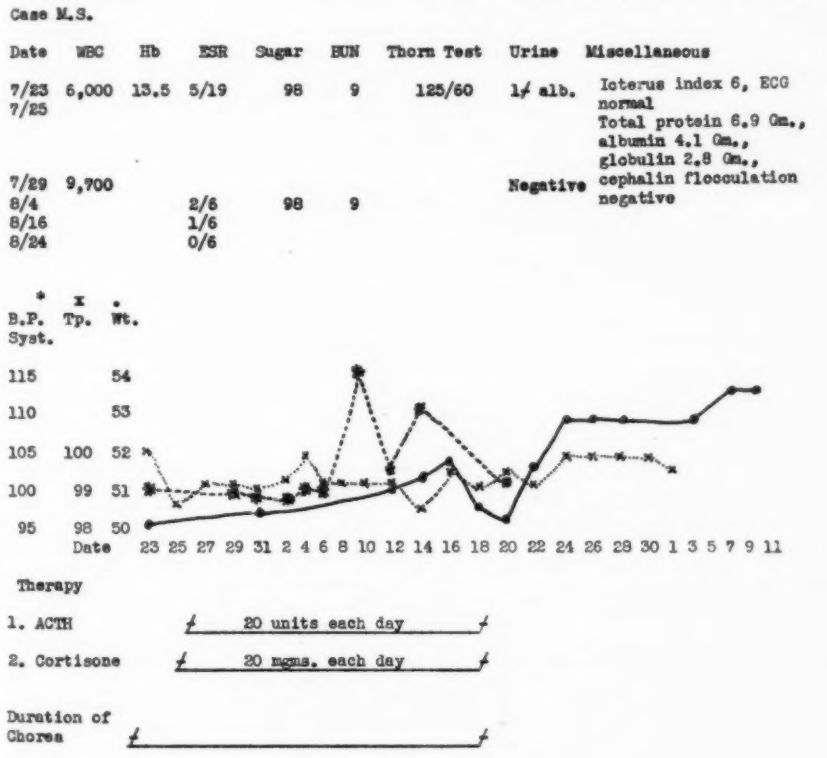
Case M.S.
Date WBC Hb ESR Sugar BUN Thorn Test Urine Miscellaneous
7/23 6,000 13.5 5/19 98 9 125/60 1+ alb. Icterus index 6, ECG normal
7/25
Total protein 6.9 Gm., albumin 4.1 Gm., globulin 2.8 Gm.,
7/29 9,700 Negative cephalin flocculation negative
8/4 2/6 98 9
8/16 1/6
8/24 0/6
* x •
B.P. Tp. Wt.
Syst.
115 54
110 53
105 100 52
100 99 51
95 98 50
Date 23 25 27 29 31 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 1 3 5 7 9 11
Therapy
1. ACTH 20 units each day
2. Cortisone 20 mgms. each day
Duration of Chorea

Fig. 1 (Case 1).

During the past year she had had several bouts of epistaxis with the last attack occurring in June, 1952. The family history was essentially negative.

Upon physical examination she manifested facial grimaces, snakelike movements of the tongue, marked athetoid movements, muscular weakness, restlessness, and irritability. In addition, there was a marked inabil-

increased to 10 mg. of each every six hours. By August 18, moonface appeared and choreiform movements were slightly diminished. Improvement continued daily so that by August 31, chorea had cleared and the medication was stopped. The patient, however, remained until September 15 because of an abscessed tooth which was extracted by the dentist prior to her discharge.

Case M.R.

Date	WBC	Hb	ESR	Sugar	BUN	Urine	Thorn Test	Miscellaneous Tests
7/29	10,000	11	2/17	90	12	Neg.		Wassermann - Negative
7/30				80	19	Neg.		
7/31	11,850	13	1/23				337/156	Total Protein 6.5 Gm., Albumin 3.8 Gm.
8/4				90	10			Globulin 2.7 Gm.,
8/13			2/30					Ceph. Floc. - Neg.
8/25			4/50					
8/28			3/31					
9/4	12,350	13	2/18					

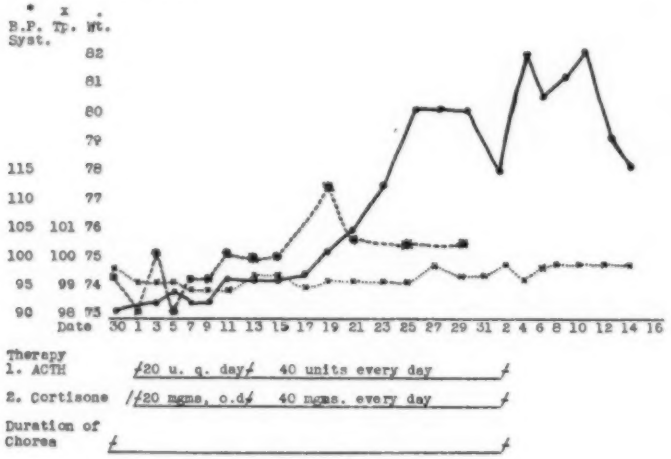

Fig. 2 (Case 2).

Case A.V.

Date	WBC	Hb	ESR	Sugar	BUN	Thorn Test	Urine and Culture	Miscellaneous Tests
6/10	8,900	9.5	23/114	90	11		Negative	Cholesterol 221, esters 135, Tot. protein 6.34 Gm.
6/12								Albumin 3.28 Gm.
6/25				92			Negative	Globulin 3.06 Gm. Sodium 144 meq.,
7/9				90			Many wbc E. coli	potassium 4.4 meq.,
7/15			7/51	82	8	123/50	E. coli	and chloride 100 meq.
7/17			7/50			50/50		
7/21	8,500			80	9	56/25	Many wbc E. coli	
7/23								
7/25			6/45					Serum phosphorus 3.4 units
7/28			17/90	148			3/ albumin	
							Many wbc and rbc	
8/4			5/34			105/87	Negative	
8/6							Negative	

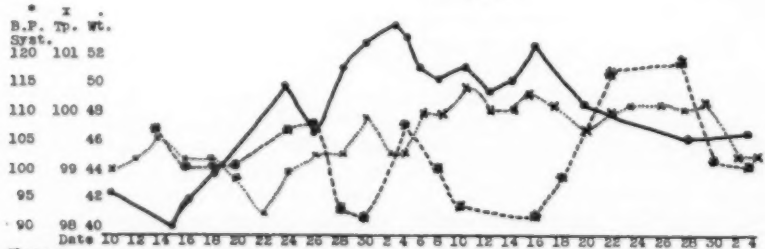

Fig. 3 (Case 3).

CASE 3.—A. V., a 6-year-old Puerto Rican female, was admitted on June 9, 1952, with a three-day history of slurred, indistinct speech, bizarre purposeless movements, marked muscular weakness, fatigue, malaise, and emotional instability.

In 1951 she had migratory polyarthritis for ten days. However, there was no other familial history of rheumatic fever.

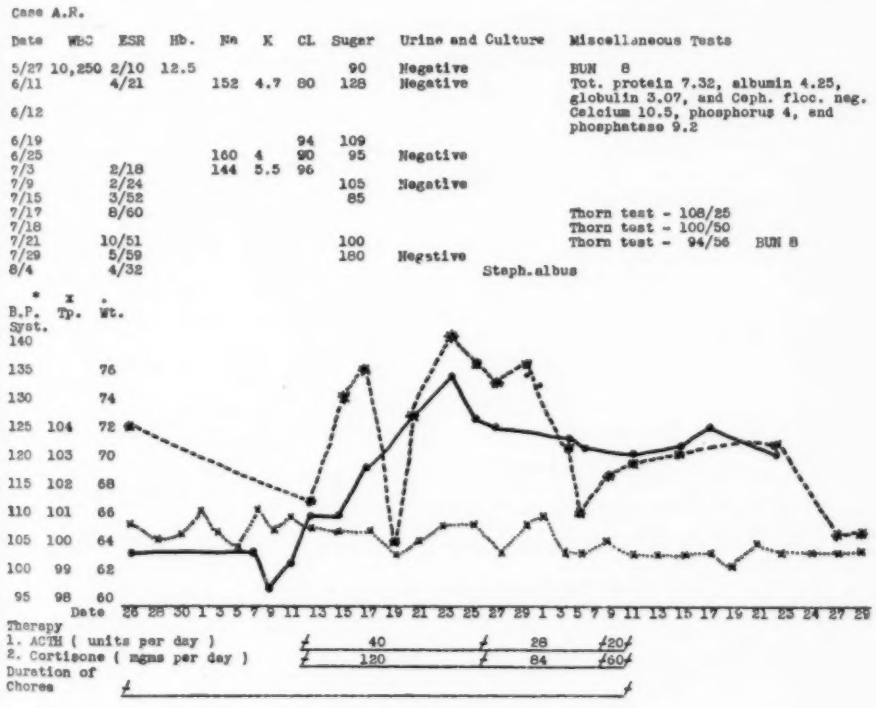
Case A.R.
Date WBC ESR Hb. Na K Cl Sugar Urine and Culture Miscellaneous Tests
5/27 10,250 2/10 12.5 90 Negative BUN 8
6/11 4/21 152 4.7 80 128 Negative Tot. protein 7.32, albumin 4.25, globulin 3.07, and Ceph. floc. neg.
6/12 Calcium 10.5, phosphorus 4, and phosphatase 9.2
6/19 94 109
6/25 160 4 90 95 Negative
7/3 2/18 144 5.5 96
7/9 2/24 105 Negative
7/15 3/52 85
7/17 8/60 Thorn test - 108/25
7/18 Thorn test - 100/50
7/21 10/51 100 Thorn test - 94/56 BUN 8
7/29 5/59 180 Negative
8/4 4/32 Staph.albus
B.P. Syst.
Tp.
Wt.
Date
Therapy
1. ACTH (units per day)
2. Cortisone (mgms per day)
Duration of Chorea

Fig. 4 (Case 4).

On physical examination fine and coarse choreiform movements of the upper and lower extremities were noted. There also were uncontrollable purposeless snakelike movements of the tongue and irregular movements of the thorax. On the following day an occasional right hanging reflex was noted. On June 13 she was placed on ACTH and cortisone therapy (ACTH 10 mg. and cortisone 30 mg. every six hours). Clinical improvement began to be noted on June 16. By July 1 there were no further signs of chorea, the hanging reflexes had disappeared, but evidence of moonface was noted. At this time therapy was discontinued.

On July 5 the patient experienced sudden, severe, coliclike pain in the epigastrium. On palpation, a tender, movable, discrete, firm mass could be felt 6 cm. below the costal border of the right upper quadrant. An intravenous pyelogram was done and revealed bilaterally enlarged renal pelves and hydroureters with kinking of the right ureter 5 cm. below the pelviureteral junction. Urine cultures on July 9, 15, and 21 all revealed *E. coli*. The patient was placed on 250 mg. of terramycin every six hours for eleven days, following which all

further urine cultures were negative. A retrograde pyelogram was done following completion of terramycin therapy and revealed a completely normal genitourinary tract. The child was discharged with a minimal moonface but no other symptoms or physical findings on August 5.

CASE 4.—A. R., an 11-year-old Puerto Rican male, was admitted with a two-month history of bizarre purposeless movements and muscular weakness. This was first noted in school when his handwriting became awkward and he constantly dropped his pencil. He became very nervous, fidgety, irritable, and cried easily. Two weeks prior to admission he developed fever for two days and pain in the shoulders and ankles, which lasted until his admission on May 26, 1952.

There was neither past nor familial history of rheumatic fever.

On admission, physical examination revealed generalized muscular weakness, especially on the left. He walked on a wide base and leaned to the left. He could not put on his shoes, and had marked purposeless movements. No hanging reflexes were noted. A soft systolic apical nonradiating murmur was heard. By May 29 the symptoms appeared to subside so that there were no outward signs of chorea. However, on June 5 he began to manifest occasional purposeless movements of his hands and wrists, his speech became slurred, and he tired easily. By June 12 he had marked choreiform movements and bilateral hanging reflexes. He was given 10 mg. of ACTH and 30 mg. of cortisone every six hours intramuscularly. Within twenty-four hours he gained 4 pounds, and by June 17 his blood pressure rose to 135/75. Therefore, he was placed on a salt-free diet. On June 20 he could

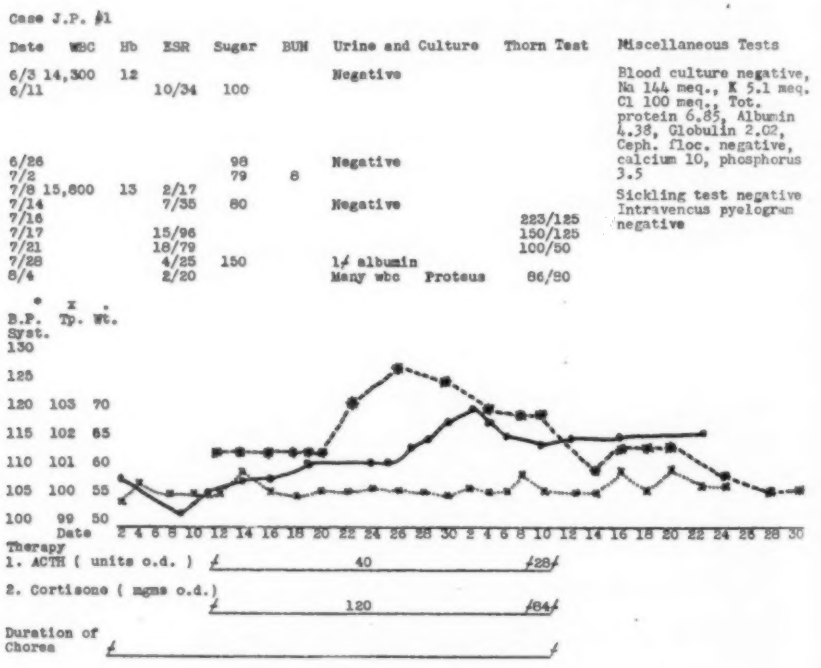
Case J.P. #1
Date WBC Hb ESR Sugar BUN Urine and Culture Thorn Test Miscellaneous Tests
6/3 14,300 12 Negative
6/11 10/34 100
Blood culture negative, Na 144 meq., K 5.1 meq. Cl 100 meq., Tot. protein 6.85, Albumin 4.38, Globulin 2.02, Ceph. floc. negative, calcium 10, phosphorus 3.5
6/26 98 Negative
7/2 79 8
7/8 15,600 13 2/17
7/14 7/35 80 Negative
Sickling test negative
7/16 223/125
Intravenous pyelogram negative
7/17 15/96 150/125
7/21 18/79 100/50
7/28 4/25 150 1+ albumin 86/80
6/4 2/20 Many wbc Proteus
B.P. Syst.
Tp.
Wt.
Date
Therapy
1. ACTH (units o.d.)
40
28
2. Cortisone (mgms o.d.)
120
84
Duration of Chorea

Fig. 5 (Case 5).

walk a straight line easily and his choreiform movements had markedly diminished, but he began to develop a moonface. Except for a lowered blood pressure, and loss of several pounds for several days while on the new diet, both the blood pressure and the weight began to rise again. Therefore, on June 26 ACTH was decreased to 7 mg. and cortisone to 21 mg. every blood pressure was normal, moonface was minimal, and he had lost 8 pounds. At this time therapy was stopped. On July 15 his erythrocyte sedimentation rate began to rise and a low-grade temperature was noted, but by August 4 the erythrocyte sedimentation rate and temperature were normal. He was discharged from the hospital on August 5 as asymptomatic.

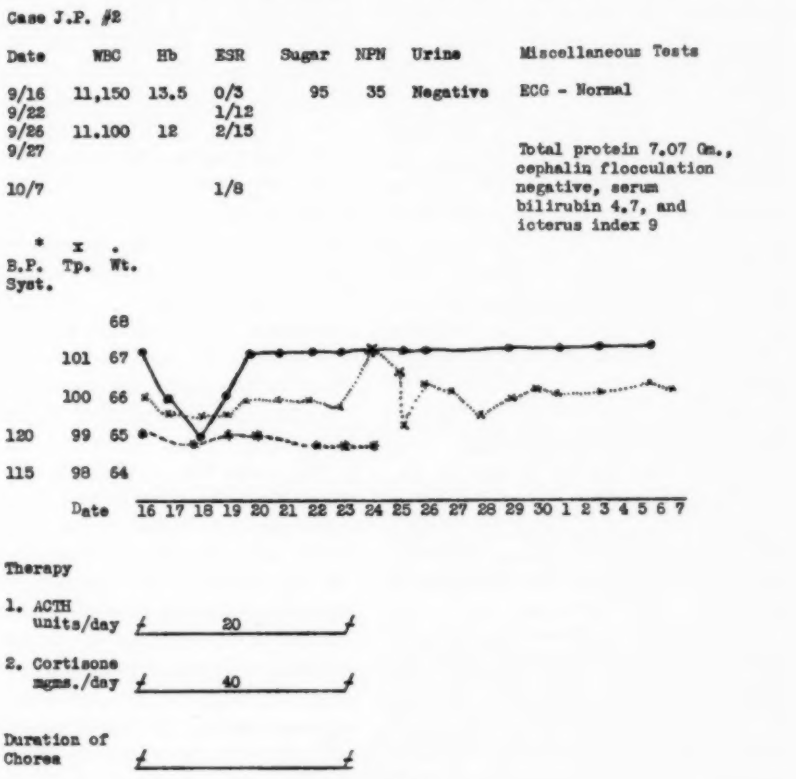
Case J.P. #2
Date WBC Hb ESR Sugar NPN Urine Miscellaneous Tests
9/16 11,150 13.5 0/3 95 35 Negative ECG - Normal
9/22 1/12
9/26 11.100 12 2/15
9/27 Total protein 7.07 Gm., cephalin flocculation negative, serum bilirubin 4.7, and icterus index 9
10/7 1/8
* x .
B.P. Tp. Wt.
Syst.
68
101 67
100 66
120 99 65
115 98 64
Date 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5 6 7
Therapy
1. ACTH units/day 20
2. Cortisone mgms./day 40
Duration of Chorea

Fig. 6 (Case 6).

six hours. Within a few days the blood pressure and weight began to go down but the moonface became very marked. For this reason his medication was again reduced to 5 mg. ACTH and 15 mg. of cortisone every six hours. Marked improvement was noted and by July 11 no further choreiform movements were detected,

CASE 5.—J. P., an 8-year-old Puerto Rican boy, was admitted on June 2, 1952, with a two-day history of headache, malaise, vomiting, vague joint pains, and nervousness.

In 1949 he was treated at another hospital for rheumatic fever and chorea, at which time he developed cardi-

tis. In March, 1950, he was hospitalized for chorea and fever.

There is no family history of rheumatic fever obtainable.

Physical examination on admission revealed a temperature of 100.2° F., a mitral systolic murmur, and generalized coarse movements of all extremities, awkward gait, bilateral hanging reflexes which were more marked on the right. The right upper extremity demonstrated the most marked choreiform movements. On June 12 the patient began to show less evidence of chorea and continued to improve gradually. Since moonface became more noticeable and weight increased, on July 9 the dosage of ACTH was decreased to 7 mg. and cortisone to 21 mg. every six hours. On July 12 no further evidence of chorea was noted and medication was discontinued. On July 19 the patient developed pharyngitis and was given 300,000 units of penicillin every twelve hours until July 28. On July 21 moonface had disappeared and a double mitral murmur now was heard. On August 5 the patient was discharged to clinic.

CASE 6.—J. P. (same as Case 5) was readmitted on Sept. 16, 1952, because of extreme weakness of his right arm, anorexia, and generalized purposeless movements of his right extremity.

On physical examination there was weakness of the right hand and arm, poor coordination, and athetoid movements of the right arm and hand while at rest. There were also purposeless movements of the right leg, which was dragged while walking. The hanging reflex was present bilaterally. ACTH and cortisone therapy was started on admission (ACTH 5 mg. and cortisone 10 mg. every six hours intramuscularly). Choreiform movements gradually diminished and on September 23 the patient did not display any further signs of chorea. On this date therapy was discontinued. The patient was discharged as asymptomatic on October 6.

The patient was seen on November 1 on an outpatient basis and again on November 18. On both visits there was no evidence of chorea aside from the persistence of the hanging reflex. However, he returned to clinic on December 15 and no evidence of chorea or hanging reflexes was noted.

For the purpose of comparison and discussion, all patients who have been reported as treated with either ACTH or cortisone are grouped chronologically in Table I, and include the present cases as well.

DISCUSSION

In the present series, every patient received medication until complete clearance of symptoms. The time for cure was considered as the interval from the day of admission until the day of cessation of therapy. Dosages were started arbitrarily, but upon the appearance of any untoward signs, the amounts were decreased with the patient's welfare as the prime consideration.

The procedure followed in this study was different from most of the others in which the medications were given for a limited time only, usually six to fourteen days, except for the second case of Aronson and associates[7] (28 days) and the one reported by Cutler[3] (fifty-six days).

In addition, although others (Aronson and associates',[7] Case 2 and Dixon and Bywaters'[5] Case 4) had used ACTH and cortisone consecutively, this was the first time that both were used simultaneously. As can be noted from Table I, five patients were treated and cleared in twenty-three, twenty-six, thirty-four, and forty-eight days, respectively. The forty-day case (J. J.) had a relapse within two months but cleared up in eight days with less medication but with a

higher relative proportion of ACTH to cortisone. Thus this makes a total of six cases treated and cleared in eight to forty-eight days with therapy being administered from seven to thirty-two days.

Ratios of 1:1, 1:2, and 1:3 of ACTH to cortisone were tried. From the limited number of cases, it would appear that when using the greater proportion of ACTH to cortisone, less medication was necessary and the patient cleared up quicker. However, this should not be considered conclusive without additional trial in the future.

There was evidence of moonface in all cases starting from eight to twenty-three days after treatment. Three patients (A. V., A. R., and J. P.) developed systolic hypertension (considering any systolic above 120 as unusual). However, upon cessation of medication, all adverse phenomena disappeared.

With regard to weight changes, the following was observed. With the lower dosage of ACTH to cortisone of 5 units to 5 mg., there was no gain in weight, but as the dosage was increased to 10:10, or greater, the weight decreased but tended to be greater than the weight on admission.

It has been shown that rebound phenomena[1, 2, 9-11] may begin several days after cessation of therapy. In Taran's and Gulotta's[11] series, this effect was evident even with decreasing dosages. In the present series, there was no evidence of rebound phenomena upon decreasing dosages. However, three cases revealed increased sedimentation rates and temperatures following complete cessation of therapy. Although at first glance this appeared to be rebound phenomena, upon rechecking the patients, each of these revealed evidence of genitourinary infections. Upon the administration of antibiotics all three patients made a complete recovery.

Three of the children (A. V., A. R., and J. P.) developed positive urine cultures with one positive for *E. coli*, another for proteus, and the third for *Staph. albus*. Except for the culture and urine, there were no other manifestations to suggest infection until therapy was discontinued. At this time, the temperature and sedimentation rates began to rise. Antibiotics cleared up the infections. The fact that 50 per cent of the cases revealed hyperglycemia without glycosuria, and genitourinary infections occurred in the same three, suggests several interesting thoughts. First, it is possible, as was recently demonstrated,[12-14] that the steroids have some effect on the renal tissue especially of growing children. Second, the fact that is known but can stand re-emphasizing is that infections may be suppressed or masked during hormone therapy. Moreover, the fact that all three had urinary infections suggests that this may be a more vulnerable area than other systems. Since these patients were all permitted the regime of modified bed rest as previously outlined,[15] the urinary infections cannot be attributed to postural factors. From these observations, it was felt that all children receiving hormone medication should have their genitourinary tract checked before, during, and after therapy to rule out any infections. Should this turn out to be as common as it appears to be in this small study, then it would be advisable to recommend the routine supplementation of hormone therapy with antibiotics.

TABLE I

AUTHOR	NO. OF PATIENT	AGE YR.	SEX	DURATION PRIOR TO THERAPY	THERAPY	MG. PER DAY	NO. DAYS THERAPY	TOTAL MG.	CHOREA CLEARED	RELAPSE	RESULT
Massel et al.[1]	1	7	M	1 mo.	ACTH	30	10	300	41 da.		S
April–May, 1950 (1 case)								975	Not cleared		U
Aronson et al.[7]	1	3	M	4 wk.	Cortisone	100	3				
Jan., 1951 (2 cases)					Cortisone	50	6				
					Cortisone	75	5				
	2	9	M	5 da.	Cortisone	150	1	2,175	Not cleared		U
					Cortisone	100	1				
					Cortisone	50	4				
					Cortisone	100	6				
					Cortisone	150	7½				
					ACTH	100	9	900			
Cutler[3]	1	12	M		Cortisone	300	1	5,725	56 da.		S
June, 1951 (1 case)					Cortisone	200	1				
					Cortisone	100	6				
					Cortisone	75	3				
					Cortisone	100	5				
					Cortisone	75	4				
					Cortisone	100	36				
Bunim[2]	1				ACTH	50-100	14	700-1,400	14 da.	1	U
Feb., 1951 (4 cases)	2				ACTH	50-100	14	700-1,400	14 da.		S
	3				ACTH	50-100	14	700-1,400	14 da.		S
	4				ACTH	50-100	14	700-1,400	14 da.		S
Kreidberg et al.[4]	1	12			ACTH	4	14	56	14 da.		S
Oct., 1951 (2 cases)	2										S
Glaser and Merritt[8]	1	13	F	1 mo.	ACTH	80	10	800	Not cleared		U
March, 1952 (1 case)											

Dixon and Bywaters[5]	1	14	F	54 da.	ACTH	50	8	400	36 da.		S
April, 1952 (4 cases)	2	14	F	21 da.	ACTH	60	3	540	48 da.		U
					ACTH	120	3				
	3	10	M	420 da.	ACTH	50	8	400	Not cleared		U
	4	8	F		ACTH	50	3	550	91 da.		U
					ACTH	80	5				
					Cortisone	100	8	800			
Kroop et al.[6]	1			28 da.	Cortisone	200-300	7	1,400-2,100	7 da.		S
Oct., 1952 (2 cases)	2			39 da.	Cortisone	200-300	?		?		U
Schwartzman, Zaontz, and Lubow	1	7	M	21 da.	ACTH	20	23	460	26 da.		S
(6 cases)					Cortisone	20	23	460			
	2	13	F	4 da.	ACTH	20	12	1,040			
					ACTH	40	20				
					Cortisone	20	12	1,040	34 da.		S
					Cortisone	40	20				
	3	6	F	3 da.	ACTH	40	19	760	23 da.		S
					Cortisone	120	19	2,280			
	4	11	M	2 mo.	ACTH	40	14	984	48 da.		S
					ACTH	28	13				
					ACTH	20	3				
					Cortisone	120	14	2,952			
					Cortisone	84	13				
					Cortisone	60	3				
	5	8	M	2 da.	ACTH	40	27	1,164	40 da.	1	S
					ACTH	28	3				
					Cortisone	120	27	3,492			
					Cortisone	84	3				
	6	8	M	5 da.	ACTH	20	8	160	8 da.		S
					Cortisone	40	8	320			

Since most textbooks[16-17] state choreas may clear spontaneously in six to ten weeks, it was felt that those cases which cleared within thirty days from the onset of therapy would be considered as successfully treated. Since three of the patients required more than 30 days to clear up, it would seem that the effectiveness of the therapy is about 50 per cent if the time element is considered, but 100 per cent if the status of the condition is considered irrespective of time. These results are better than those obtained in the previous cases reported and reviewed in Table I. Of the latter seventeen cases, nine were considered by their authors as successfully concluded while eight were failures. Actually, however, three of the successful cases required thirty-six, forty-one, and fifty-six days, respectively, and if the thirty-day limit is considered as the successful therapeutic index,[18] then the ratios would have to be altered to six favorable against eleven unfavorable. With this correction for time, then only 33 per cent actually responded on the individual hormone method as against 50 per cent on the combined therapy.

However, in considering cure regardless of time, of the twenty-three total cases to date, fifteen have been successful and eight unsuccessful. From the number of cases treated thus far, the efficacy of hormones cannot yet be clearly stated. However, it would seem from the amount of material available at present, that the combined form of therapy is somewhat superior to the individual type. Of course, larger series must be studied before any dependable conclusions can be reached. Furthermore, much more work must be done on the variations of the combination to determine the optimum ratio.

SUMMARY

1. Six patients with chorea were treated simultaneously with ACTH and cortisone for the first time.

2. Medication was continued until the symptoms cleared.

3. Results appeared to be better than with individual therapy or with time-limited therapy.

4. Maximum therapy required was thirty-two days.

5. All cases cleared from eight to forty-eight days when calculated from the day of admission rather than from the first day of therapy.

6. The better results appeared to occur with combinations in which the ACTH-cortisone ratios approached each other.

7. Infections may be latent and progress during therapy so that antibiotics may be beneficial additions to the therapy.

CONCLUSION

This study revealed the superiority of combined hormone therapy over their individual administration in chorea. However, this finding should not be considered as an implication that hormone therapy is the preferred or acceptable one for this condition. On the other hand, it should act as an added stimulus for their further evaluation and justification for their utilization in this situation.

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THE TREATMENT OF PINWORM (ENTEROBIUS VERMICULARIS) INFECTION WITH BACITRACIN AND SULFASUXIDINE

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THE pinworm, *Enterobius vermicularis*, is one of the most prevalent parasites of man and it is also one of the most difficult worms to eradicate. The simple life cycle of the parasite with its peculiar adaptation to the habits of civilized man facilitates spread of the infection despite elaborate modern sanitary facilities. Gentian violet, probably the cheapest, safe and effective agent against the pinworm, has an efficacy of from 60 to 90 per cent. It is, however, not well tolerated by some patients, especially young children who may also experience difficulty in swallowing the enteric-coated tablets. The side effects, though not serious, are often disturbing enough to result in discontinuation of the treatment. Wells and associates,[1] on experimental evidence of the activity of terramycin against the mouse pinworm, tried this antibiotic against pinworm in man and found it to be effective. This was confirmed by Loughlin and associates,[2] and others[3, 4]; the cure rate for terramycin, according to the reports, varies from 85 to 100 per cent depending on the dosages employed and the criteria of cure. Our studies using bacitracin against both natural[5] and experimental infections[6, 7] of the mouse oxyurids indicate that this antibiotic is also effective. Goddard and Brown[8] treated fifteen cases of enterobiasis with oral bacitracin and on the basis of two Scotch tape swabs taken seven to fourteen days after treatment found that 40 per cent were freed of their pinworms. Chan tested bacitracin against the mouse pinworm Syphacia, which has a life cycle similar to Enterobius, and he also demonstrated the synergistic action of some of the poorly absorbable sulfonamides with this antibiotic. He found that the addition of either Sulfasuxidine or sulfaguanidine to bacitracin therapy increased the efficacy of treatment five to ten times as determined by the removal rate of pinworms from infected mice. The present investigation was designed to determine the value of the bacitracin-Sulfasuxidine combined therapy against enterobiasis in man.

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METHODS

The diagnosis of enterobiasis was established by the presence of eggs of *E. vermicularis* on the Scotch tape swabs from patients, and treatment was initiated as soon thereafter as possible. On the completion of treatment, the patients were instructed to submit one swab every other day for two weeks and one swab per week for another two weeks, totaling nine posttreatment swabs in a month's period. All pre- and posttreatment swabs were made by the patients or a member of their household who was instructed in

the proper technique of securing the specimens. The patients were also instructed in the essential hygienic measures to prevent reinfection. In view of the brief life cycle of *E. vermicularis*,[9] it was decided to assess the results of treatment from swabs taken in the three-week period after treatment. The appearance of Enterobius eggs in the swabs after the third week may not indicate failure of treatment as reinfection may become evident at this time. Our criteria of cure is based on the evidence of six or more consecutive swabs negative for Enterobius eggs.

DOSAGES

Regimen I

Adults: Bacitracin 120,000 units daily, in four doses for five days.
Sulfasuxidine 6 Gm. daily, in four doses for five days.

Children: Bacitracin 10,000 units per 10 pounds weight daily, in three or four doses for five days.
Sulfasuxidine 500 mg. per 10 pounds weight daily, in three or four doses for five days.

Regimen II

Adults: Bacitracin 120,000 units daily, in four doses for seven days.
Sulfasuxidine 3 Gm. daily, in four doses for seven days.

Children: Bacitracin 10,000 units per 10 pounds weight daily, in three or four doses for seven days.
Sulfasuxidine 250 mg. per 10 pounds weight daily, in three or four doses for seven days.

To facilitate a valid comparison of the effect of bacitracin with and without the simultaneous administration of Sulfasuxidine, the daily doses of the antibiotic employed in both regimens were identical to those used by Goddard and Brown.

The patients ranged from 1 to 52 years in age and they were referred to us by several local physicians. Many had harbored the pinworm for long periods of time and had proved refractory to various pinworm chemotherapeutic agents.

RESULTS AND DISCUSSION

Six adults and eleven children were given the bacitracin-Sulfasuxidine combined therapy for five days (Regimen I) (Table I). Thirteen of these seventeen patients were found to be free of Enterobius after treatment. Three of the four unsuccessfully treated patients were given a second course of therapy and two were subsequently found to be cured. The eleven patients given the combined therapy for seven days (Regimen II) (Table II) included three adults and eight children; all except one were cured. This child gave only one positive swab eight days after completing treatment. The cure rate computed for those receiving a single course of the five-day treatment was 77 per cent, while for those who were given therapy for seven days, a 91 per cent cure rate was obtained (Table III). All of the patients tolerated the drugs well although several experienced loose stools, but none was disturbed to the extent of having to interrupt treatment. Most of the patients reported a clinical improvement after treatment, and four patients who had complained of anal pruritus were relieved of the symptom.

Combining the two groups of patients treated five or seven days, we obtain a cure rate of 82 per cent for the group of twenty-eight, compared to the 40 per cent cure rate reported by Goddard and Brown[8] who gave bacitracin alone in the same dosage we employed, but who continued it for fourteen days.

Sisk[10] administered 2 to 8 Gm. of Sulfasuxidine daily for seven days to

TABLE I. RESULTS OF FIVE-DAY COURSE OF BACITRACIN-SULFASUXIDINE THERAPY (REGIMEN I) ON ENTEROBIUS VERMICULARIS IN MAN

CASE NO.	SEX	AGE	NUMBER NEGATIVE SWABS POSTTREATMENT WEEKS 1	2	3	4	5	6	TOTAL	COMMENT
1	M	39	1	4	2	1			8	Cure
2	F	36	3	4	1	1			9	Cure
3	M	11	3	4	1	1			9	Cure
4	F	8	P	P						Failure
5	M	4		4	3				7	Cure
6	M	24	2	2	P	P			4	Failure
7	F	52	3	4	1				8	Cure
8	F	3	1	4	1				6	Cure
9	M	2	1	4	1				6	Cure
10	M	6	3	3	1				7	Cure
11	M	5	3	3	1				7	Cure
12	M	Adult	1	1	2	1	1		6	Cure
13	F	Adult		1	2	2	1		6	Cure
14	M	Child		1	2	2	1		6	Cure
15	F	Child		1	2	2	1		6	Cure
16	M	Child		P						Failure
17	F	1	P	P						Failure
18*	F	6	2	2					4	Insufficient follow-up
19*	F	10	1	2					3	Insufficient follow-up
			Second course of treatment							
4	F	8	4	2	1				7	Cure
16	M	Child	3	2	1				6	Cure
17	F	1	P	P						Failure

P = positive swab.
*Not included in the computation of results.

TABLE II. RESULTS OF SEVEN-DAY COURSE OF BACITRACIN-SULFASUXIDINE THERAPY (REGIMEN II) ON ENTEROBIUS VERMICULARIS IN MAN

CASE NO.	SEX	AGE	NUMBER NEGATIVE SWABS POSTTREATMENT WEEKS 1	2	3	4	TOTAL	COMMENT
1	M	39	3	3	1		7	Cure
2	M	4	3	3	1		7	Cure
3	M	Adult	2	3	1		6	Cure
4	F	Adult	3	3	1		7	Cure
5	M	9	2	3	1		6	Cure
6	M	7	3	3	1		7	Cure
7	F	6	2	2	1		5	Cure
8	M	6		1	3	2	6	Cure
9	F	3	2	2	1		5	Cure
10	M	8	2	P			2	Failure
11	F	4	2	2	2		6	Cure

P = positive swab.

TABLE III. A COMPARISON OF FIVE-DAY AND SEVEN-DAY COURSES OF BACITRACIN-SULFASUXIDINE THERAPY ON ENTEROBIUS VERMICULARIS IN MAN

	NO. PATIENTS TREATED	NUMBER CURED	PER CENT CURED
Regimen I: 5 days	17	13	77
Regimen II: 7 days	11	10	91

TABLE IV. COMPARISON OF THE EFFICACY OF BACITRACIN, SULFASUXIDINE, AND BACITRACIN-SULFASUXIDINE AGAINST THE PINWORM OF MAN

	NO. PATIENTS TREATED	NUMBER CURED	PER CENT CURED
Bacitracin therapy (Goddard and Brown)	15	6	40
Sulfasuxidine therapy (Sisk)	56	Few	Not computed
Bacitracin-Sulfasuxidine (present study)	28	23	82

fifty-six patients harboring Enterobius and repeated the course after a week's rest period. Because of the numerous positive swabs returned from the patients in the three-week follow-up period, the author did not attempt to determine the exact percentage of cure but reported few successful treatments. Table IV summarized the results of these studies, and it appears that the simultaneous administration of bacitracin and Sulfasuxidine is more effective in removing pinworms than either agent employed alone.

The mode of action of bacitracin and Sulfasuxidine on Enterobius is unknown. It is possible that these agents alter the bacterial flora of the host and thereby deprive the pinworm of some necessary food or metabolite. They may also act directly upon some vital process of the parasite. Bacitracin and Sulfasuxidine are not inexpensive drugs and relatively large amounts are required for the treatment of pinworm, which will greatly restrict their usefulness.

SUMMARY

Bacitracin and Sulfasuxidine, when administered simultaneously, are effective in the removal of the pinworm of man. Treatment for five days produced a 77 per cent cure rate, while a seven-day course apparently cured 91 per cent of the patients. The combined therapy is more effective than either agent employed alone against enterobiasis.

The authors wish to thank Commercial Solvents Co. for the bacitracin and Sharp & Dohme for the Sulfasuxidine used in this study.

We also wish to thank Drs. H. B. Shookhoff and M. Sterman of the Tropical Disease Diagnostic Service, Department of Health, City of New York, for the inclusion of six patients treated in this clinic.

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EFFECTS OF RUBEOLA ON TUBERCULOSIS

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AN EPIDEMIC of rubeola at the Children's Pavilion of Seton Hospital, a municipal tuberculosis institution for New York City, led us to investigate the effects of the disease on childhood tuberculosis.

Much data have been published relative to the results of infectious diseases on tuberculosis. Many authors have observed that the endemic illnesses like rubeola, pertussis, and influenzal and pneumococcal infections were followed by phthisis. Constantino[1] in 1932 reported from the German, French, and Italian literature many cases whose anamnesis revealed a previous infectious disease. He reported that rubeola and pertussis are frequent releasing causes.

The evidence seemed that these diseases, along with diabetes, increased the receptivity of the soil for invasion.[2] Such illnesses reduced the resistance of the individual and produced favorable conditions for activation of a dormant foci of tubercle bacilli, or the spreading of already active minor foci. It was the impression that any disease causing irritation of the mucous membrane or defects in the epithelium facilitated activation.[3] Rubeola has been repeatedly quoted as favoring spread or activation of tuberculosis.[4, 5]

A reduction in tuberculin allergy was most constant in rubeola as described by von Pirquet and others.[6, 7] Ribadeau-Dumas[2] and others[8] discussed the other phthisiogenic diseases producing anergy. This loss of tuberculin hypersensitivity, during or after the infection, modified the response of the tubercle bacillus causing a predisposition, resulting in acute dissemination.[3]

Infectious diseases have been overestimated as a cause or predisposing factor for the spread of tuberculosis.[9, 10, 11, 12] Berghoff[13] conducted a survey at Camp Grant in 1918 on a large series of young adults (596) and found only one patient showed unmistakable signs of activation of old tuberculosis. In the past few decades it has come to be considered that rubeola is not harmful in tuberculous children.

An outbreak of measles in January, 1952, afforded us the opportunity of studying the effects of this disease on childhood tuberculosis. None of the cases of rubeola was severe. All but two were transferred to the Willard Parker Hospital when the diagnosis was made and were subsequently returned to Seton.

Thirteen cases of rubeola developed in a group of approximately eighty tuberculous children. After the initial spread of the epidemic, gamma globulin was given to the rest of the children.

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In our series of thirteen cases, there were the following clinical types:

Type	*Total*	*Active*	*Inactive*
Primary, simple	5	4	1
Primary, pleural	1		1
Primary, hilar bilateral	1	1	
Primary, progressive	6	6	
	13		

There were six males and seven females. The age distribution ranged from 2 to 4½ years.

It is extremely difficult to determine clinically the nature of the pulmonary change. All of the thirteen patients did well. No gastric cultures became positive. The children showed weight gains.

No complications of rubeola or of tuberculosis developed in the group. The two arrested primary cases were transferred to a Preventorium after two and five months of observation, and the other eleven were observed for seven months following measles.

Roentgenograms were studied carefully during the period of observation. A listing of the cases is given in Table I.

COMMENT

We noted no spread of the tuberculous process in any of the thirteen cases and there was a definite regression of the lesion in four patients. Of the six progressive primary cases, four received some streptomycin therapy, one received Rimifon therapy. All the progressive primary cases were on PAS. The two stable cases received no medication.

TABLE I

CASE	SEX	NO.	AGE (YR.)	TYPE	WEIGHT GAIN	CULTURE	THERAPY	X-RAY
1. M. B.	F	1483	2½	Prog. LUL, A	0	N	S, PAS	Regression
2. W. E.	M	1497	3	Prog. RU & LL, A	1	N	PAS	Slight regression
3. L. L.	F	1235	2¾	Simple RLL, A	2	N		Regression
4. A. B.	M	1060	4	Simple RML, A	3	N	PAS	No activation
5. A. J.	F	1258	2½	Hilar, Bilateral, A	3	N		No activation
6. J. R.	M	1061	4	Prog. LUL, A	5	N	S, PAS	No spread
7. L. S.	F	1118	4½	Simple RML, A	5	N	PAS	Regression
8. L. M.	F	1259	2¼	Simple LUL, A	3	N		No activation
9. O. U.	M	1236	4½	Prog. RLL, LH, A	1	N	S, PAS	Stable
10. P. W.	M	1500	3	Prog. RML, A	2	N	Rimifon	No spread
11. W. R.	M	1454	2¾	Prog. RUL, A	0	N	S, PAS	No change
12. Y. C.	F	1381	2	Simple RM & UL, I	0	N		No activation
13. D. M.	F	1415	4	Pleural, I	8	N		No activation

S, streptomycin.
PAS, para-aminosalicyclic acid.
A, active.
I, inactive.
RUL, Right upper lobe.
RU & LL, Right upper and lower lobe.
RML, Right middle lobe.
RLL, Right lower lobe.
LUL, Left upper lobe.

SUMMARY

The effects of rubeola were noted and studied in thirteen children with primary tuberculosis. The children were observed for a period of seven months.

No specific effects were noted on tuberculosis.

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BONE MARROW ASPIRATION SITES IN INFANTS AND CHILDREN

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IT IS obvious that a choice of marrow biopsy sites is advantageous. In our experience the choice of the bone marrow aspiration site varies with the age of the child.

We have found the tibia a very satisfactory source for marrow of infants and children up to age 2 years. The ilium has been useful in apprehensive patients of any age, especially in older children and adults. The sternum is hematopoietically active throughout life and is readily accessible in a cooperative patient. Other less commonly used sites are the spinous processes of the vertebrae, the rib, the femur, and the humerus.

Several factors determine which area or whether more than one area will be used. The degree to which the patient cooperates will influence the decision as to which site is most readily and safely biopsied. A very apprehensive patient may show less anxiety during biopsy of the ilium than the sternum. Occasionally it is desirable to secure a specimen from a particular bone if it contains a localized lesion. Frequently it is useful to check an additional site to determine whether a given specimen is representative. The experience and technique of the operator frequently influence the choice of biopsy site. In general, marrow specimens from various sites in the same patient are comparable.[1-5]

The sternum remains hematopoietically active throughout life and for this reason it is, for many hematologists, the choice source of marrow. Also it is a superficial bone which is easily accessible in a cooperative patient. Although the sternum of the infant is largely cartilaginous, cancellous bone is found to be almost constantly present in the body of the sternum at the level of the second interspace. Most physicians prefer this area of the sternum.* Although the manubrium may provide an equally good marrow specimen, it is our experience that with the vertical approach of the needle, the proximity of the chin offers a mechanical disadvantage. The sternum of a crying infant is less accessible when the child presents a heaving chest, and one feels he is approaching a moving target under the patient's chin. Also, in the case of small children when cooperation is lacking, the sternum seems less safe.

The ilium is frequently preferred by the apprehensive patient and has been reported to have been used successfully in patients of any age.[1] In our experience we have found that aspiration of iliac marrow may be difficult in some newborn and small infants, although we experience no difficulty in obtaining a specimen from the sternum or tibia of the same patients.

It was observed in the case of some infants that when an attempt was made

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*Studies of the sternum[6, 7] show that the ossification centers appear in pairs; the ossification centers of the manubrium ordinarily fuse at birth; those paired ossification centers of the sternebrae are not completely fused until 8 to 10 years of age. For these anatomical reasons some prefer the site of puncture to be just off the midline at the level of the second interspace.

to infiltrate the periosteum of the ilium with the procaine needle, a sensation of penetrating a substance comparable to art gum was felt. Curiosity led to examination of a newborn pelvis obtained at autopsy of an apparently normal stillborn. A rim of cartilage 7 mm. deep extended throughout the entire length of the iliac crest and when a procaine needle was inserted into it the sensation described above of penetrating a soft tissue was again experienced. The area of the ilium containing marrow was found to be in the iliac fossa far below the iliac crest. The thickest part of this area was only 3 mm. and the inner and outer periosteal layers occupied much of the 3 mm., leaving a narrow or shallow marrow cavity.* The needle used for procaine infiltration was inserted at right angles to the marrow cavity and the bevel of the needle extended beyond the periosteum in both directions. Obviously successful aspiration of marrow from the ilium in this newborn infant would have depended upon penetrating the iliac crest between the leaves of the two periosteal layers to enter the small area containing marrow. One could penetrate periosteum and cartilage and miss obtaining a specimen of marrow. Although the epiphyses of the iliac crest do not appear until puberty or later,[8, 9] successful biopsy in children younger than this is usual. In adults the crest of the ilium offers too great a resistance to be practical for penetration and a site is chosen 1 cm. below the iliac crest.

We have used the tibia frequently as a marrow aspiration site in infants and children under 2 years of age. Caronia[10] reported in 1922 that he found this site practical. The tibial marrow remains active and is a representative site in early childhood. Fat replacement becomes prominent about the seventh or eighth year of life.[6, 7]

The site[11] of puncture is a flat triangular area at the proximal end of the medial surface of the tibia. It is inferior to the medial epicondyle and medial to the tibial tuberosity.

The tibia is more easily immobilized than the other bones for marrow sites. It is helpful to place the child on a firm supporting surface such as an examining table. If the hip is abducted and the knee flexed, one can hold the lower leg firmly supported throughout its entire length and exert the necessary pressure for needle penetration without fear of injuring the knee.

Both the lateral and the dorsal surfaces of the spinous process have been used as a source of marrow.[2, 3] Loge[2] reported comparable specimens from the sternum and the spinous processes of twenty-five adults. The spinous processes of the vertebrae of the stillborn infant which we examined were largely cartilaginous.*

Block and Jacobson[12] recommended surgical biopsy of marrow from lesions in ribs in Gaucher's disease. The femur has been used as a source of marrow in some clinics.[13, 14, 15]

The reader is referred to other reports for details of equipment needed,[16] the techniques used for aspiration,[6, 7, 16, 17] the preparation of the marrow for study,[16-22] and the in-

*Scammon[8] described the periosteum in newborn infants to be one-third to one-half the actual thickness of periosteum in the adult. He also mentions that 60 per cent of the skeleton of the newborn infant is made up of material other than osseous tissue.

*Scammon[8] described the vertebrae of the newborn infant to be composed of three separate osseous masses (a bony body and two lamina) connected by hyaline cartilages. The two lateral masses fuse in the midline during the first year of life. The epiphyses of the vertebrae appear after puberty.

terpretation of findings.[6, 7, 13, 16, 23-26] Only a brief comment for equipment and technique is included here,

Aspiration Procedure.—The site for biopsy is located and prepared with a local antiseptic and sterile drape. The skin and periosteum are infiltrated with 1 per cent procaine. The needle is inserted vertically until the tip touches the periosteum. Then the guard is screwed down until it is flush with the skin. Following this, the guard is turned back two and one-half to three turns. This provides the added length needed for penetration of the marrow cavity.[1, 2, 18] The outer table of bone is penetrated by a rotary movement under firm pressure. In some cases a "give" is felt when the bone has been penetrated and the needle is in the marrow cavity. When the needle is firmly fixed in the sternum, the stylet is removed and a syringe attached and aspiration attempted by rapid suction.[1] This may be the most painful part of the procedure, and it is helpful to instruct the nurse, who is restraining the child, to tighten her hold.

Needle.—For sternal marrow aspiration in infants and small children, a miniature model[16] of the University of Illinois sternal needle* is made from a 17 gauge spinal needle. This is a modification of the original Klima-Rosseger needle. It is equipped with a rotating guard designed for use in preventing penetration of the inner lamina of the sternum.

The larger type needle such as is used in adults is entirely satisfactory for the tibial aspiration biopsy at any age.

Preparation of the Marrow.—It is ordinarily preferable to take 1 c.c. in older children and 0.2 to 0.5 c.c. in infants and small children. More than this amount will represent an excessive dilution with sinusoidal blood. Actually only a drop or two is needed for direct smears of the marrow. As soon as the smears are made the slides are dried rapidly in front of a fan or by rapid whipping through the air. They are stained with any common blood stain such as Wright's or May-Grünwald Giemsa. If volumetric studies are to be made the 1 c.c. volume provides a constant technique producing relatively similar quantitative data. For details of this procedure refer to references[16, 17, 19, 27, 28].

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SUMMARY

It is obvious that a choice of marrow biopsy sites is advantageous. The sternum is hematopoietically active throughout life and is readily accessible in a cooperative patient. The ilium has been useful in apprehensive patients of any age especially in older children and adults. The tibia has been, in our experience, a satisfactory site in the newborn infant and in children under 2 years of age. Other less commonly used sites are the spinous processes of the vertebrae, the femur, and the humerus.

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HAMARTOMA OF THE HYPOTHALAMUS

Report of Two Cases With Associated Developmental Defects

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THE term "hamartoma" is generally used for a tumor that is due to overdevelopment of tissue normally found at the site of the neoplasm. Reports of hamartomas of the hypothalamic region are rare and those found in the literature were published primarily because of the effect of the growth on the development of the sex organs. In the two cases presented here, no evidence of premature sexual development was found. One of the children had a cleft palate as well as evidence of mental retardation, and the family history revealed additional instances of mental deficiency and of lesions involving the nervous system. In the other case the hamartoma was associated with congenital heart disease.

CASE REPORT

Case 1.—D. M. H. was born May 22, 1950. This was the fifth pregnancy of a 26-year-old white woman. The mother was in good health and the pregnancy as well as the delivery was uneventful except for polyhydramnics. The infant weighed 6 pounds 10 ounces and had a fronto-occipital circumference of 13.25 inches. Respiration was spontaneous but of a grunting character and there was some cyanosis. The infant was placed in an incubator and oxygen started. The respiration soon became normal and the cyanosis disappeared.

Examination a few hours later showed a restless male infant who preferred to lie on the side with the head arched backward, the neck hyperextended. There was a partial cleft palate. The grasp reflex was present. A chest x-ray was negative. Five hours after birth the infant suffered a generalized convulsion and had six more such seizures in the next two and one-half days. These were controlled with phenobarbital. X-rays of the skull, a urinalysis, and a blood count were normal. A lumbar puncture resulted in a "bloody tap"; the smear and culture were negative. During the next few days the infant improved slowly. On June 3, 1950, a cisternal puncture showed clear fluid, 7 lymphocytes, sugar 66 mg. per cent, protein 65 mg. per cent, smear and culture negative. On July 3, 1950, the infant was admitted to St. Joseph's Infirmary with a history of twitchings of the upper extremities, muscular stiffness, refusing feedings, and "blue spells." On the day of admission he had become stuporous and developed fever, 104.6° F. rectally. Examination showed a dehydrated, malnourished infant who was obviously mentally defective. He still preferred to lie on the side with his head arched backward. A blood count, urinalysis, chest x-ray, lumbar puncture, and blood culture showed no abnormal findings. He was given parenteral fluids, gavage feedings, penicillin intramuscularly, and chloramphenicol orally. He rapidly improved and was discharged July 6, 1950.

At home he was described as having "drawing spells," being difficult to feed, failing to gain, not progressing normally, and having fever from time to time. He was readmitted to the hospital Sept. 25, 1950, in about the same condition as before. Skull x-rays and a urinalysis were negative. Ad-

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mission blood count showed 13,850 white cells with 60 per cent neutrophils. Before discharge the white count dropped to 5,600 with 38 per cent neutrophils. He was given parenteral fluids, gavage feedings, and penicillin intramuscularly. He weighed 6 pounds 10 ounces on admission and 7 pounds 8 ounces on discharge Oct. 9, 1950. Fronto-occipital circumference was 14.75 inches. During the hospital admission his neurological status did not change but his general physical condition was improved by the various supportive measures.

He was readmitted to the hospital from Oct. 15 to 19, 1950, with similar findings and a similar course. The last admission was from Nov. 22 to 23, 1950. He had been growing progressively worse. In addition to the previous findings there were scattered medium moist râles, slight cyanosis, and the liver edge was palpable two fingerbreadths below the right costal margin. Death occurred on Nov. 25, 1950.

Family History.—The mother's first and second pregnancies resulted in normal children. The infant resulting from her third pregnancy was apparently normal the first two months. By the age of 3 months hydrocephalus was noted. When 7 months of age he was operated upon for hydrocephalus and expired the same day. Necropsy showed internal hydrocephalus. The infant resulting from the fourth pregnancy ran a clinical course similar to D. M. H. He was cared for by one of us. He expired at home at 2 months of age. Permission for necropsy was not obtained.

A brother of the father of D. M. H. and a sister of the mother of D. M. H. are married. The first pregnancy resulted in a miscarriage. The second pregnancy resulted in a girl who died at the age of 5 months. Her clinical course was similar to D. M. H. Necropsy is said to have shown a "mature glioma of the brain stem." The third and fourth pregnancies resulted in normal children.

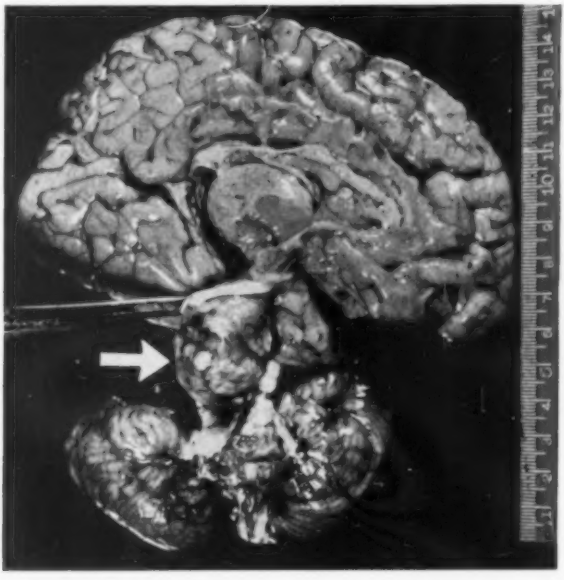

Fig. 1 (Case 1).—Arrow points to a rounded mass which occupies the region of the infundibulum and is attached to the optic chiasm. Note knoblike projection apparently representing deformed mamillary body.

Fig. 2.

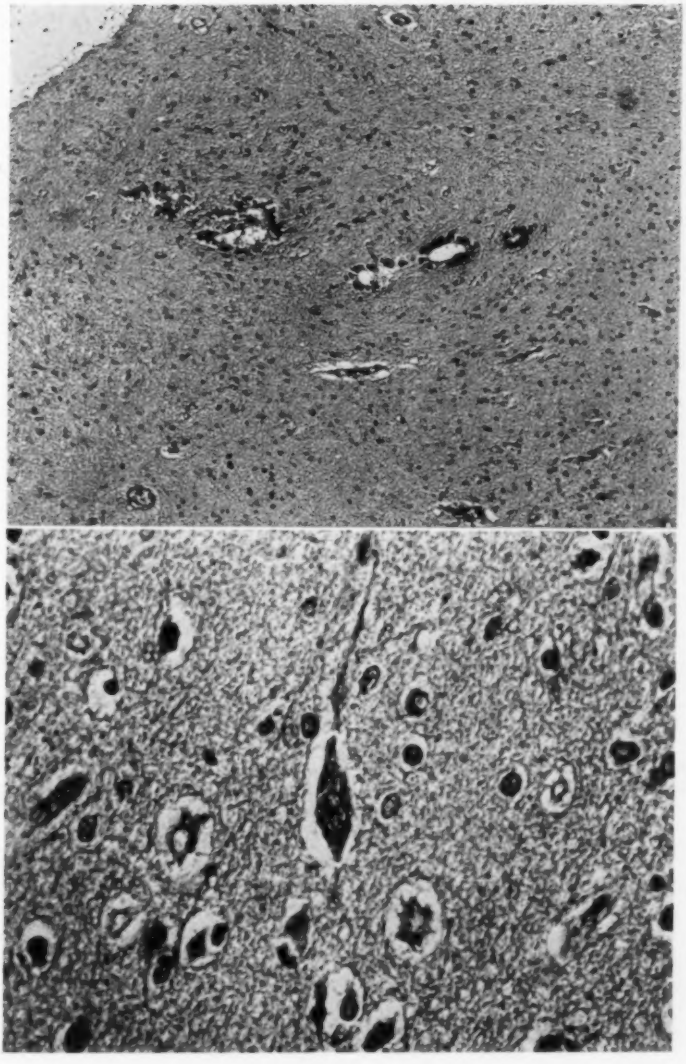

Fig. 3.

Fig. 2 (Case 1).—Section from the mass shows several spaces lined by ependyma. (H and E ×100, reduced ⅛.)

Fig. 3 (Case 1).—High-power view demonstrates ganglion cells and glia. (H and E ×430, reduced ⅛.)

Post-mortem Findings.—Autopsy was performed two hours after death (A-50-173, St. Joseph's Hospital). Only pertinent findings are given here.

The body was that of an underdeveloped, poorly nourished infant weighing 4,000 grams and measuring 62 cm. from crown to heel. The occipitofrontal circumference was 38 cm. There was marked widening of the fontanels and also some separation of the sutures of the skull. Marked serotal edema was noted as well as edema of the lower extremities. The brain weighed 700 grams and bulged markedly beneath the meninges. Numerous petechiae were found within the white matter of both hemispheres and the corpus callosum. A rounded mass, averaging 2.5 cm. in diameter, occupied the region of the infundibulum and filled the interpeduncular fossa. It encroached upon the cerebral peduncles and also was intimately attached to the optic chiasm, which showed pressure atrophy. The third ventricle was compressed and the lateral ventricles were dilated. The mamillary bodies could not be identified.

The tumor tissue varied from tan to pink. It was firm in its posterior portions while it showed gradual transition into the soft brain substance at its anterior pole. A flat rounded structure was loosely attached to the lower surface of the mass. It measured 0.4 cm. in diameter and lay just above the pituitary fossa. The fossa itself appeared shallow and contained only a minimal quantity of soft, friable tissue.

Sections from different portions of the brain, including the cerebellum, showed multiple petechiae within the white matter. Most of these were in the vicinity of distended capillaries. In the cerebellum, the majority of these hemorrhages were located at the border zone between the white and gray matter. The tumor that was grossly described for the floor of the third ventricle consisted of myelinated fibers and a network of glial fibers with numerous typical glial cells. These cells had uniform appearing, rather small nuclei, and were in general diffusely distributed except for a few foci where there seemed to be crowding of the glial cells. Also present within the mass were ganglion cells which appeared to be mature, although some of them were slightly atypical. In some of the sections, several narrow cavities lined by ependymal cells were present. Moderate vascularity was found throughout the lesion and the vascular structures were within normal limits. The tissue of the optic chiasm was found to be in close association with the surface of the mass and showed evidence of compression atrophy. No relation to the pituitary was demonstrated.

The final diagnosis was: hamartoma of hypothalamus, hemorrhagic encephalopathy, bilateral bronchopneumonia, mural thrombus of right auricle, and fatty metamorphosis of liver.

Case 2.—B. R. P., a white female aged 5 years, was admitted to Memorial Hospital Feb. 3, 1950, with a complaint of recurrent attacks of cyanosis and unconsciousness since birth. These attacks had become progressively more severe and upon admission she had been unconscious for twelve hours.

The patient was a "blue baby" and activity had been limited during her entire life. Several episodes of mild decompensation had been noted and recently a shunting operation was considered. She had numerous upper respiratory infections and greatly enlarged tonsils. The only other previous illness was mumps. At the time of the birth of the patient both parents were aged 39. There is one brother living and well, aged 16 years.

On admission, the patient was cyanotic; blood pressure was 90/40, pulse 130 per minute and irregular, respirations 50 per minute and shallow. The other positive findings included an enlarged heart with a to-and-fro murmur, moist râles over both lung bases, clubbing of the fingers and toes, and an enlarged liver. The musculature was flaccid. The genitals were normal

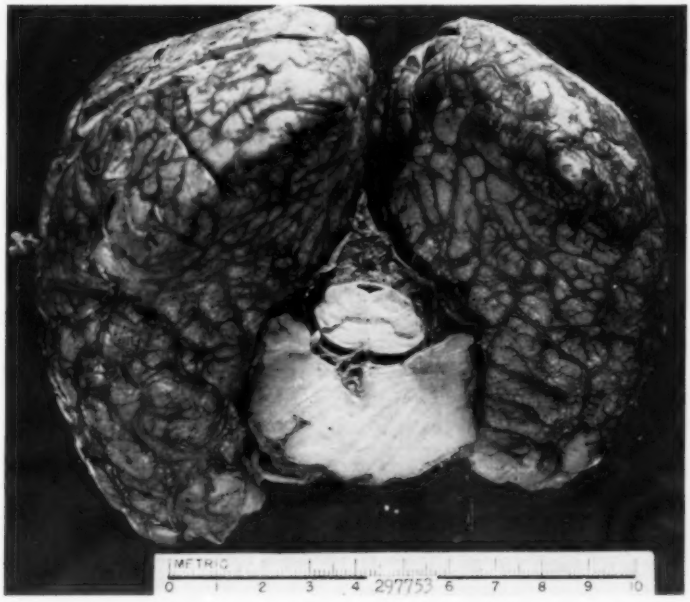

Fig. 4 (Case 2).—Coronal section reveals a large, well-circumscribed mass at the base of the brain. (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

Fig. 5 (Case 2).—Representative section from the mass, showing large ganglion cells and many glial elements. (H and E, ×170, reduced ⅓.) (Courtesy Armed Forces Institute of Pathology, Washington, D. C.)

female and there was no evidence of precocious puberty.

The erythrocyte count was 5,510,000 and there were 16 grams of hemoglobin, 18,700 leukocytes with a differential count of 36 segmented forms, 63 lymphocytes, and one eosinophil. Urinalysis was acid, specific gravity was 1.010, one plus albumin, negative sugar, and 3 to 6 coarsely granular and 6 to 8 finely granular casts per high-power field. A chest roentgenogram showed clear lung fields and gross enlargement of the heart. An electrocardiogram showed right axis deviation.

Following admission she regained consciousness but there were many periods of mental cloudiness and stupor. On February 7 the patient was again comatose with flaccid paralysis of all extremities, bilateral positive Babinski and ankle clonus. The temperature ranged from 99° to 101.8° F. Treatment included administration of fluids, digitalis, and oxygen. Terminally respiratory stimulants were given. She expired Feb. 8, 1950.

Only the pertinent autopsy findings are included (A-7-50, Memorial Hospital). The body was that of a well-developed white female and there was no evidence of precocious puberty. There was cyanosis and clubbing of the fingers. The heart was enlarged and showed the tetralogy of Fallot. The thymus was not enlarged and there was no increase in fluid in the serous cavities. The pericardial surfaces showed a few petechiae. The liver was enlarged and congested. No lesions were noted in the ovaries.

The brain showed marked congestion, particularly of the superficial cerebral vessels and of the choroid plexuses in the lateral ventricles. The convolutions of the cerebral cortex were well formed and the sulci of the usual depth and width. The cerebral hemispheres were symmetrical. The ventricles were symmetrically placed and not enlarged and they contained a considerable amount of serosanguineous fluid.

There was a large well-circumscribed mass lying at the base of the brain and extending from the level of the upper medulla oblongata to a point just caudal to the optic chiasma. It lay in the midline and measured 6.5 x 6 x 2.3 cm. It was relatively symmetrical, with a firm gray-white smooth glistening surface. At the level of the lower pons there was some separation into two lobules. The mass was well demarcated from the pons and its dorsal surface was separated from the ventral aspect of the brain stem by meninges and the basilar artery. Ventrally the mass was covered by meninges which were continuous with those over the cerebellum. Superficially there were many congested vessels and the surface had the gross appearance of cerebral cortical tissue. The left optic nerve showed lateral displacement and the trigeminals were at the inferior aspect of the mass. There was broad connection of the mass to the anterior portion of the hypothalamus. The hippocampi were present with some apparent sclerosis on the right. The mamillary bodies showed no gross changes. There was some flattening of the fornix. The pituitary gland was slightly concave and showed marked congestion. The sella turcica showed no destructive changes.

Microscopic sections showed capillary thrombi in the heart, lungs, and brain. There was marked generalized congestion of the viscera. The architecture of the pituitary was well preserved and there was marked congestion.

In sections of the cranial mass there were normal-appearing meninges with greatly dilated vessels. Superficially the glia was dense with three to five underlying laminae. The neurons were diffusely scattered, variable in shape, and generally large. Deeper there were many large astrocyte nuclei and some oligodendroglia with a few fibers throughout the sections. The Weigert myelin sheath stain showed myelinated fibers which in some areas were in bundles radiating downward from the superficial part of the mass. The

Bodian stain showed many axis cylinders running in various directions near the surface but in parallel bundles deeper in the mass.

The tissue was interpreted as an hamartoma mimicking cerebral cortex. Other brain sections showed some apparent increase in the number of capillaries in the cerebral cortex and generalized congestion.

DISCUSSION

The subject of hamartoma of the hypothalamus has been recently reviewed by Richter[1] and it would be superfluous to give again a complete account of the literature. There are several points of particular interest in our two cases and these will be compared with the previously published reports.

A striking feature of Case 1 is the presence of anatomical defects of the central nervous system in two siblings and in one cousin. Sections from the tumor in the case of the cousin are rather incomplete, but resemble those from the hamartoma presented here by the presence of mature ganglion cells. The lesion lay in the brain stem, the maximum involvement being in the pons. It was said to have extended upward into the mesencephalon so that a possible origin from the hypothalamus cannot be ruled out. Of the anatomical findings in Case 1, the relatively large size of the lesion and the evidence of increased intracranial pressure are of interest. There was no invasion of any of the neighboring structures but there was pressure atrophy of the peduncles and of the optic chiasm. The knob-like structure at the ventral aspect of the mass is interpreted as a malformation of a mamillary body and is considered strong evidence in favor of a developmental origin of the lesion rather than a true neoplasm.

In Case 2, the lesion was even larger, but was demarcated from the structures of the base of the brain except for the hypothalamus to which it was connected by a broad base.

Richter,[1] after a critical review of the literature, recognizes only three records of indubitable examples of true hamartomas, and adds one of his own. Meyer's[2] case, although rejected by Richter, is for purposes of comparison included in this discussion since its

TABLE I

AUTHOR	PATIENT'S AGE AND SEX	GREATEST DIAMETER OF LESION	ASSOCIATED DEVELOPMENTAL DEFECTS	PRECOCIOUS SEXUAL DEVELOPMENT
LeMarquand and Russell[3]	5 years Male	1.5 cm.	None	Present
Driggs and Spatz[4]	3 years Male	1 cm.	None	Present
Bronstein, Luhan, and Mavrelis[5]	22 months Female	0.4 cm.	None	Present
Meyer[2]	13 years Female	"Small apple"	None	Present
Richter[1]	7 years Female	1 × 0.7 cm.	None	Present
Authors' Case 1	6 months Male	2.5 cm.	Cleft palate	Absent
Authors' Case 2	5 years Female	6.5 cm.	Tetralogy of Fallot	Absent

features, as described by the author, seem quite similar to the other reports.

Comparison with the previously published instances reveals our two cases to be the only ones in which evidence of precocious sexual development was lacking. They also differ from all but one of the others by the large size of the hamartomas, that of Case 2 being apparently the largest on record. The excessive size of the mass might, together with the relatively young age of the patients, furnish the clue to the absence of secondary sex changes as there was pressure atrophy of the hypothalamic centers rather than stimulation by the hamartoma which is generally accepted for the other cases. The association with other congenital defects is in line with the concept of this lesion as a malformation which is further enhanced, in Case 1, by the pronounced familial tendency toward developmental abnormalities of the central nervous system.

A clinical diagnosis of hamartoma of the hypothalamus cannot be expected to be made with any degree of accuracy. If precocious sexual development is a part of the clinical picture, the possibility of a hamartoma should be included in the differential diagnosis. It suggests itself particularly if there is, in addition, evidence of increased intracranial pressure, of other malformations or a history of congenital lesions of the nervous system in other members of the patient's family.

SUMMARY

Two new cases of hamartoma of the hypothalamus are reported. Neither was associated with precocious sexual development in contrast to the five cases collected from the literature. Additional developmental defects were present in both patients. In Case 1 there was also a history of various defects of the central nervous system having been present in two siblings and in one cousin of the patient.

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EMBRYONAL CELL CARCINOMA OF THE LIVER IN INFANCY

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THERE is a difference of opinion as to what constitutes an acceptable example of primary hepatic carcinoma in a child. In a review of hepatic carcinoma in children, Steiner[1] found seventy-seven acceptable cases, including two of his own in patients up to 16 years of age. Wells[2] was more skeptical and excluded three of the cases included in Steiner's series. Bigelow and Wright[3] in their review of the cases also excluded the cases found to be unacceptable by Wells and listed ninety-five well-documented cases.

It is the purpose of this communication to add to the literature a case of primary carcinoma of the liver in an infant. When the number of reported cases becomes adequate, a thorough review will be possible and will result in a better understanding of this entity.

CASE REPORT

F. B., a 9-month-old white female infant, was admitted to the Binghamton City Hospital on Jan. 9, 1952, with progressive abdominal enlargement and distention of two weeks' duration. The infant was able to eat until one day prior to admission when she started to vomit after feedings, the vomitus consisting of undigested food. She had normal bowel movements until one day prior to admission, following which bowel movements ceased even after repeated enemas. There was no history of hematemesis, melena, or tarry stools. Physical examination revealed a well-developed, well-nourished white female infant with a temperature of 102° F. rectally. On abdominal palpation, a large mass was found to be present, occupying the entire right side of the abdomen from the right costal margin to a point below the anterior superior iliac spine. The mass was oval in shape and smooth except for a firm nodule which was palpable on the anterior surface of the mass. The percussion note over this mass was dull while the remainder of the abdomen was tympanitic. Peristalsis was hypoactive.

Blood count revealed a red count of 2.84 million cells per cubic millimeter, hemoglobin of 52 per cent or 8 grams, color index of 0.92, and a white count of 21,020 with a normal differential except for a slight shift to the left. The urinalysis was normal. Impression of a flat plate of the abdomen was a large, soft-tissue mass which appeared to be continuous in the right upper quadrant. The exact etiology was undetermined but the possibilities suggested were large liver cyst, omental cyst, and retroperitoneal tumor. This mass was interpreted on barium enema as a retroperitoneal tumor displacing the ascending colon and the hepatic flexure forward. Intravenous pyelogram was normal and an upper gastrointestinal series revealed a mass of water-density type displacing the duodenal bulb and the stomach upward, to the left and anteriorly.

The infant developed a progressive anemia and her course was rapidly downhill. Exploratory laparotomy was performed on Jan. 14, 1952, and upon entering the abdominal cavity, bloody fluid and a large mass which was confluent with the liver was encountered. No definitive surgery was performed. The infant was in critical condition and she expired the following day.

From Binghamton City Hospital.

Fig. 1.

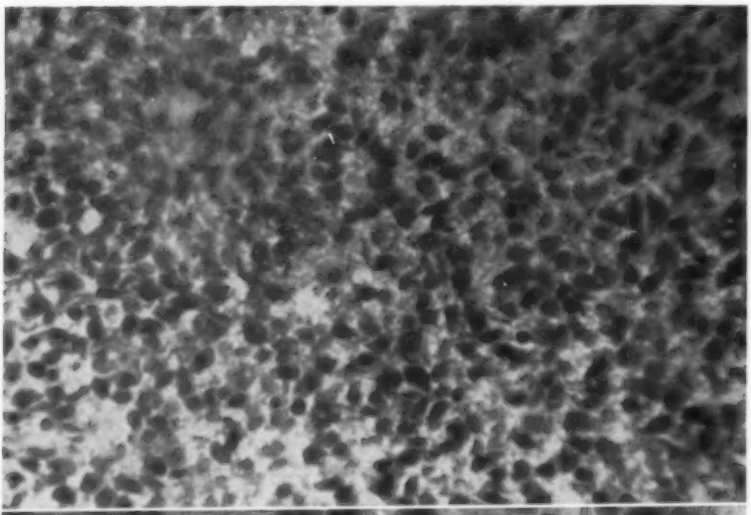

Fig. 2.

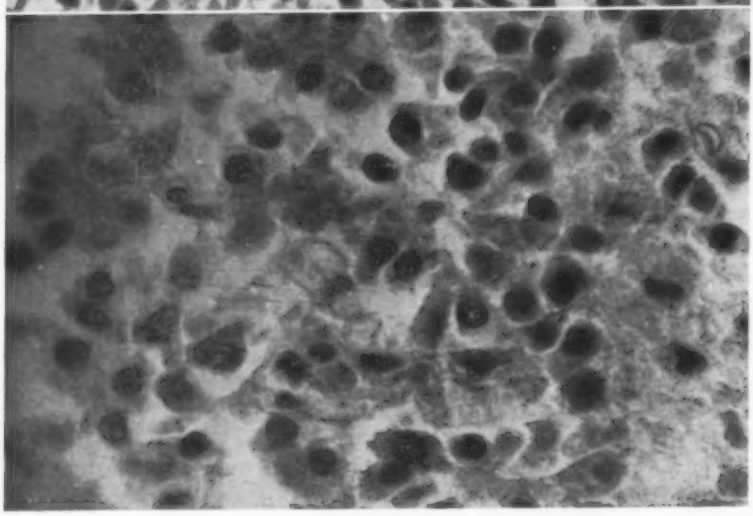

Fig. 1.—Tumor cells connected in large sheets. (3×43.)
Fig. 2.—Tumor cells elongated or round in shape with deep-staining, oval-shaped nuclei. (3×95.)

At post-mortem examination,* the abdominal cavity contained 200 c.c. of bright red fluid. There was a large mass in the right upper quadrant continuous with the liver which occupied the greater part of the right side of the abdomen and which displaced the bowel.

The liver weighed 800 grams. On the free margin of the liver, there were

*By Dr. J. S. Grewal, Pathologist, Binghamton City Hospital.

numerous, firm nodules, the largest of which measured 12 cm. in diameter. These nodular areas were yellowish-white in appearance while the remainder of the liver was a normal reddish-brown color. On cut section, the tumor mass consisted of multiple nodules of firm, grayish-pink tissue which appeared to have necrotic central areas. There were numerous recent areas of hemorrhage and cystic areas containing clotted blood. The remainder of the necropsy examination failed to show any abnormalities or evidence of metastasis.

Microscopic sections taken from different portions of the tumor revealed a very cellular, embryonal type of tumor which consisted of small, deep-staining cells showing varying characteristics, such as: (1) Areas in which the cells were connected in large sheets with numerous thin-walled sinusoids scattered throughout in an indefinite manner. These cells were slightly elongated or round in shape and contained deep-staining, oval-shaped nuclei. The remaining portion of the cells contained fairly abundant basophilic cytoplasm. (2) Areas in which tumor cells formed narrow cords arranged irregularly and which were separated by thin-walled blood vessels. These cells were elongated or cuboidal in shape. (3) Areas in which tumor cells were more definitely arranged in cords according to the normal architecture of the liver lobule but the staining character of the cells was still that of a basophilic type of cell showing undifferentiated features. (4) Areas in which a portion of a lobule was well formed but the remaining portion consisted of undifferentiated cells, the two types of tissue gradually merging into each other. (5) Areas where the sinusoids were greatly distended and the intervening cords of hepatic cells were atrophic. (6) Areas containing connective tissue with branching bile capillaries without cellular elements suggesting aplasia of the hepatic cells with only the presence of the proliferating bile capillaries. (Figs. 1 and 2.)

DISCUSSION

In a review of the literature by Bigelow and Wright,[3] ninety-five cases of primary carcinoma of the liver were listed and of these, liver-cell origin was recorded in more than sixty-one cases and bile-duct origin in only three cases. They further classified the series and listed twenty-one of these cases as "teratomas." Extrahepatic metastasis was noted in twenty-eight of the ninety-five cases, representing 29.5 per cent. The first evidence of the neoplasm appeared before the age of 2 years in fifty-five cases and in thirty-five cases, more than one-third of the total, the first symptoms developed at or before the age of one year.

In the case described in this report, the carcinoma was liver cell in origin and there was no evidence of "teratoid" structure or metastasis. The clinical manifestations were mainly abdominal distention, a nodular right-sided abdominal mass, and anemia in a female infant 9 months old. The picture in this case and the cases described in the literature are similar and characteristic. In infants presenting a right-sided abdominal mass accompanied by anemia and progressive abdominal distention, primary carcinoma of the liver should be considered.

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SICKLE-CELL ANEMIA WITH UNUSUAL BONE CHANGES

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NEW ORLEANS, LA.

BONE changes in sickle-cell anemia have frequently been reported, but those in short tubular bones of children have received little notice. This unusual feature of sickle-cell anemia in infancy was recently encountered:

A previously healthy one-year-old Negro girl was admitted after sudden onset of diarrhea, fever, and "yellow eyes" two days previously. The birth, neonatal, developmental, feeding, and social histories contributed nothing of apparent importance. Inquiry into the family background revealed no known examples of sickle-cell disease; there were no siblings.

At admission the baby appeared acutely ill. Temperature was 102° F. (r), pulse 148 per minute, respirations 40 per minute, weight 8.9 kilograms. Icterus of sclerae and mucosae was obvious, along with some pallor. Many small freely movable nodes were present in the anterior and posterior cervical triangles. There was a soft blowing systolic murmur at the apex; this seemed most likely functional in nature and was considered to be of the "hemic" type. The abdomen was protuberant, and a rounded liver edge was felt 2 cm. below the right costal margin; the spleen was not palpable. The remainder of a routine examination contributed no helpful information.

Her hemoglobin level was 5.5 grams per cent, and red blood cells numbered 2.1 million per cubic millimeter; there were 13,950 white blood cells per cubic millimeter—66 per cent of these were polymorphonuclear cells, 28 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. Ninety-five per cent of the red blood cells in a wet preparation were sickled at twelve hours. The sedimentation rate of the red blood cells was 33 mm. in an hour (Wintrobe). The diagnostic parameter was positive, in that the difference in sedimentation in oxalated blood treated with oxygen and with carbon dioxide was 44 mm.[1] The urine was dark yellow in color, and contained 1 plus albumin and a trace of sugar; specific gravity was 1.015 and the sediment showed an occasional granular cast. Test for urobilinogen was positive in a dilution of 1:10. Serum bilirubin was 13.4 mg. per cent total and the level of total protein was 6.51 gram per cent with an albumin/globulin ratio of 3.49/3.2. Cephalin-cholesterol flocculation was 1 plus, and the thymol turbidity was 16.2. The serum calcium was 5.37 and the serum phosphorus 2.6 meq. per liter. Tuberculin skin tests and serologic tests for syphilis were negative. An electrocardiogram was interpreted as being within normal limits.

She was given oxygen by tent, and aqueous penicillin injections. Subsequently she received two small transfusions totaling 200 c.c. over three days, no single transfusion exceeding 10 c.c. per kilogram; there were no reactions observed. Her diarrhea abated, and she appeared to be doing well, but on the thirteenth day obvious swelling of the hands and feet appeared (Fig. 1, *A*). The fingers were definitely tender over the puffy areas, and they felt warmer than the rest of the body, but no redness was noted.

Roentgenograms of the hands revealed areas of radiolucency in distal metaphyses of the radius and ulna as well as in the metacarpals and phalanges (Fig. 1, *B*). These were both

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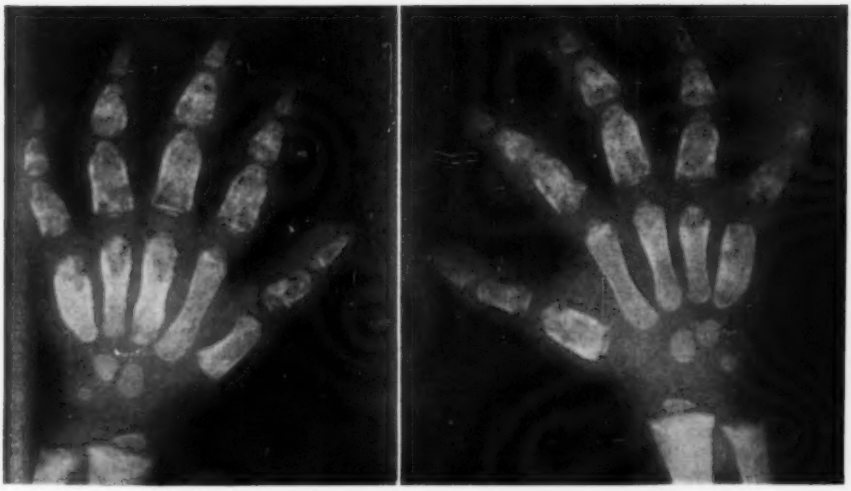
subperiosteal and intramedullary. There was evidence of expansion of the bone, but no evidence of new bone formation was found. Roentgenograms of the other long bones, chest, skull, and feet were within normal limits.

After twenty-two days the tenderness subsided, and the swelling decreased. She was then followed as an outpatient, and two and one-half months later there was still minimal puffiness; however, roentgenograms of the hands at that time showed com-

A.



B.

Fig. 1.—*A*, Appearance of hands on twentieth day; note symmetrical fusiform swellings, increased pigmentation over joints. *B*, Roentgenogram taken at same time as *A*. Note progressive intensity of involvement proceeding distally, and that most of the swelling noted in *A* appears to be due to medullary expansion in phalanges.

plete resolution to normal bone structure without deformity. At a visit six months later, all swelling had completely disappeared, and there was no jaundice though the patient was still pale; the hemoglobin level was 8.5 grams per cent, and there were 3 million red blood cells per cubic millimeter. The cardiac murmur had disappeared. Again roentgenograms of the hands and other bones showed no abnormalities.

DISCUSSION

Swelling of the hands and feet with severe changes in the short tubular bones is indeed rare in sickle-cell anemia.[2] Changes in the skull, however, have long been recognized as relatively common and are similar to those seen in other forms of chronic anemia of hemolytic origin. Vogt and Diamond[3] had suggested in 1930 that similar features might be seen in Cooley's anemia, sickle-cell anemia, and hemolytic icterus, and specifically referred to changes in the metacarpals and metatarsals. They did not include any example of sickle-cell anemia with these changes. Caffey[2] has stated that significant changes in the tubular bones are rarely demonstrable in infants and children who suffer from sickle-cell anemia, and adds that marrow hyperplasia in the long bones is less apparent than in Cooley's anemia.

Almklov, Hansen, and Scheider[4] have recently re-emphasized dual processes in sickle-cell anemia—hyperplasia of the marrow together with vascular thromboses—resulting in subsequent necrosis, hemorrhage, fibrosis, calcification, and new bone formation. Of these two processes, medullary hyperplasia is probably more common in children, the roentgenogram showing a wide medullary cavity and a thin cortex. Their patient had extensive changes, including a pathologic fracture of the femur; swollen hands and feet were also noted.

Grinnan[5] reported "peculiar striations" in the metacarpals of a 4-year-old child with sickle-cell anemia. Moore[6] had previously described obliteration of the medullary cavities in the second row of phalanges of the hand and in the metatarsals and phalanges in a young adult.

Danford, Marr, and Elsey[7] described a Negro male infant with "puffiness of the hands associated with increased local heat and tenderness" and with severe changes demonstrated on roentgen examination. A roentgenogram taken twenty-seven days later revealed none of the changes previously seen.

Macht and Roman[8] found coarse trabeculations, and periostitis or destruction in the bones of the hands or feet in five of seventeen cases and reported in detail such changes in the metatarsals of an infant with complete recovery. Carroll and Evans[9] described similar alterations in the metatarsals of a one-month-old boy with recovery after one month.

We have been unable to find other reports of the swelling of the hands and feet of infants and children with sickle-cell anemia having such striking roentgenologic features. Those described in our patient are otherwise not dissimilar to those of others, and rapid healing was again demonstrated.

SUMMARY

An infant with sickle-cell anemia had swelling of the distal extremities and remarkable roentgenographic alterations in the bones of the wrists and hands. A brief review of scattered previous reports indicated that such manifestations are probably not extremely rare, that their pathogenesis is far from clear, but that healing of the osseous lesions is usually prompt.

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Clinical Conference

CONFERENCE AT COMMUNICABLE DISEASE DEPARTMENT, CHILDREN'S HOSPITAL, SAN FRANCISCO, CALIF.

MARCH 31–APRIL 14, 1953

INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

EDWARD B. SHAW, M.D., PRESIDING

DR. SHAW.—This Clinical Conference will be presented in two sections, each comprising a one-hour discussion. The first section deals with some unfortunate end results in purulent meningitis. We have come to expect good end results with modern treatment in these diseases, but because of their very nature, unfortunate end results will sometimes be encountered in every series of sufficient size. Dr. Levin will present in brief two cases which were rapidly fatal.

DR. MARCIA LEVIN (Assistant Resident, Communicable Disease Service).—The first of these patients is a Negro male child, 2 years of age, admitted 2 A.M., Jan. 10, 1953, with a history that he had been fairly well except for mild upper respiratory infections until the day before admission when he seemed lethargic and spent the day in bed. He did not vomit and took fluids by mouth most of the day. He was seen by a physician at 6 P.M. who found nothing remarkable on physical examination and placed the child on treatment with aspirin. At 8 P.M. large black and blue spots were noted by the mother which first appeared on one ear and then were observed scattered over all four extremities. His mother telephoned the hospital late at night and the child was brought into the emergency room at 2 A.M. with a temperature of 37.5° C. but with profound prostration. He was covered almost from head to foot with purpuric spots. There were no meningeal signs. His extremities were cold and clammy, and the subcutaneous tissue seemed abnormally firm. The diagnosis was promptly recognized, and he was given intramuscular penicillin and cortisone. An effort was made to administer intravenous sulfadiazine by means of a cut-down but he died before this was completed. Autopsy showed bilateral adrenal hemorrhage, extensive purpura of the skin and mucous membrane, and patchy atelectasis of the lungs.

Our second rapidly fatal case was a nine-year-old boy who had been well until 10:30 A.M. of the day prior to admission at which time he developed a shaking chill, headache, and drowsiness. That evening he was seen by his physician who discovered the presence of numerous petechiae, performed a spinal puncture which disclosed a spinal fluid with only 17 cells per cubic millimeter, and referred the child to Children's Hospital without further medication. The trip to the hospital consumed about four hours. During this time the patient developed profound shock which was combated en route with the administration of plasma.

At entrance examination he was found to be comatose, cyanotic, and with an intense diffuse purpuric eruption. His apical heart rate was 188, there was no perceptible pulse or blood pressure. He was promptly given 400,000 units of aqueous penicillin, 2.5 Gm. of sulfadiazine intravenously, and 100 mg. of cortisone intramuscularly. He showed slight improvement during the first hour after admission and after four hours was given 50 mg. more of cortisone and 400,000 units of aqueous penicillin. His condition rapidly worsened and he expired less than eight hours after admission. Anatomical diagnosis at autopsy was meningococcemia, extensive adrenal hemorrhage, generalized lymphoid hyperplasia, and moderately hypoplastic bone marrow.

DR. SHAW.—Both of these cases illustrate sudden death in meningococcus disease in which the interval between diagnosis and death is too short for therapy to be effective. They bring up the question of the best possible treatment for this acute emergency. Sulfonamides, penicillin or other antibiotics, cortisone, and other supportive measures are effective only if the patient lives long enough for them to act. Some of us will remember the days when we used serum for treatment. Meningococcus antiserum was originally a crude product which was surprisingly effective. Serum was gradually refined to the point where it had great antibacterial potency in the laboratory but was clinically ineffective. Subsequently, and just prior to the sulfonamide era, Ferry and Hoyne reintroduced a serum of excellent antitoxic power which was of considerable clinical value. The antitoxic properties of antimeningococcus serum sometimes produce dramatic results in just such cases as those described. The one I remember best was a child who was treated by Dr. Thelander; he entered the hospital moribund in deep coma but by the time he had received a large intravenous dose of antiserum he had begun to rouse and finally survived.

In the treatment of fulminant cases the problem is to keep the patient alive until he can respond to the specific therapeutic agents which have supplanted the serum. I wrote to Parke-Davis & Company to ask if there was any way we could get hold of some antitoxin for use in just such cases but they replied that antitoxin had been so completely displaced by sulfonamides and penicillin that it was uneconomic to produce and had been nonprocurable for the last five years. Cortisone is perhaps our best answer in this medical emergency and this I have asked Dr. Kinsell of the Institute for Metabolic Research to discuss.

DR. LAWRENCE W. KINSELL.—For more than two years we have been working with combined administration of ACTH and cortisone on the one hand and with intensive antibiotic therapy on the other in the management of patients with very severe infectious conditions. With your permission I shall go over a few of the basic principles involved in such combined therapy.

In Fig. 1, in highly diagrammatic form, is shown the original observation of Dr. Max Finland of Boston. In the fall of 1949 he gave ACTH to a patient with pneumococcus pneumonia to see what would happen. This patient had a positive blood culture and the full clinical picture of severe pneumonia. After twenty-four hours of treatment

with ACTH alone, the patient was clinically well but still had a positive blood culture. The blood culture did not become negative for almost five days (the earliest time at which crisis might have occurred in the pre-chemotherapy days).

On the basis of this observation, which seemed to us a most exciting one, we contrived a working hypothesis to the effect that adrenal steroids of ACTH or cortisone or both might help to tide a patient over a period of extreme crisis. This concept is shown in Fig. 3. It was found that when such combined therapy was used, morbidity was markedly reduced in patients with a variety of illnesses and in some instances at least, mortality probably prevented.

The question arose as to how such an "antitoxic" effect might be exerted.

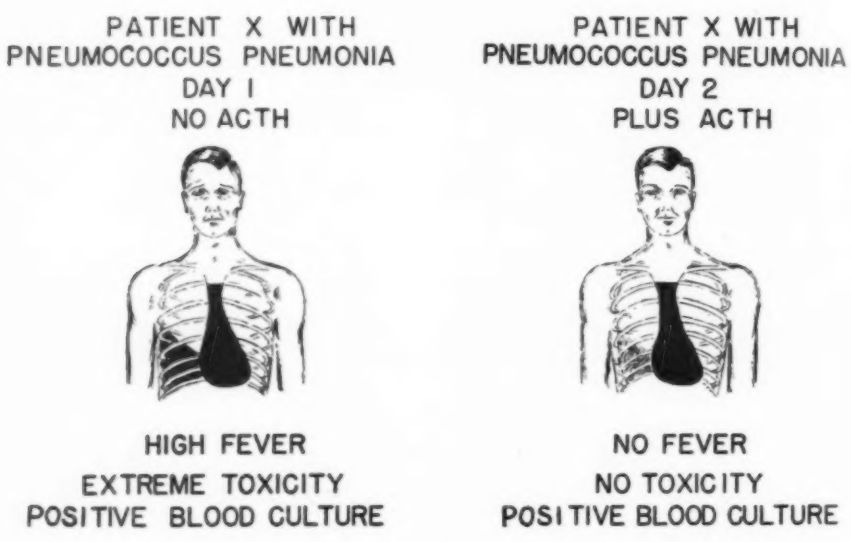

Fig. 1.

the cortisone type acted in a sense as "nonspecific antitoxins," interposing a block between a variety of bacterial and nonbacterial toxins and the peripheral cells of the patient, without in any way interfering with the growth of any organism. This concept is shown in Fig. 2. In view of this, it was felt that in very ill patients in whom for any reason antibiotic therapy alone was not considered fully adequate, at least for initial therapy, that a brief period of treatment with

In Fig. 3 are shown some of the possible mechanisms, i.e.:

1. By direct adsorption of toxins, with globulins or other materials released from lysed monocytic cells or eosinophils.

2. By effect upon cell membranes, preventing the entry of toxins into cells.

3. By protective effect of some sort upon enzyme systems within the cells themselves.

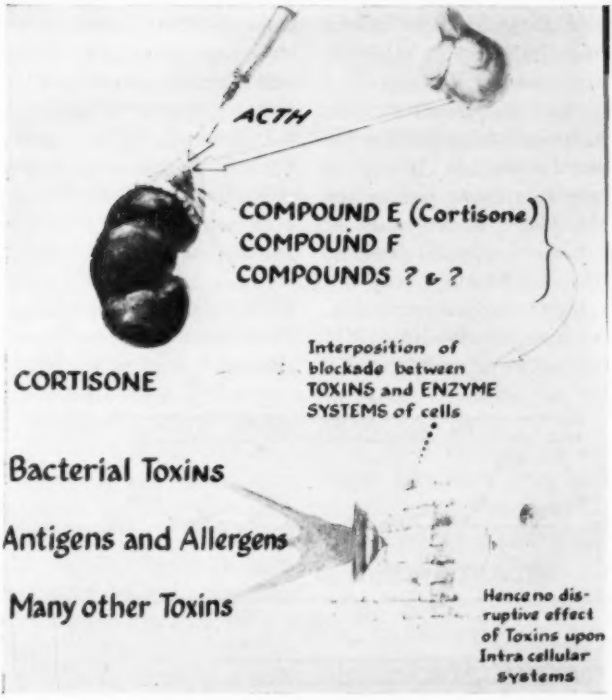

Fig. 2.—Nonspecific antitoxic action of ACTH and cortisone in acute toxemias.

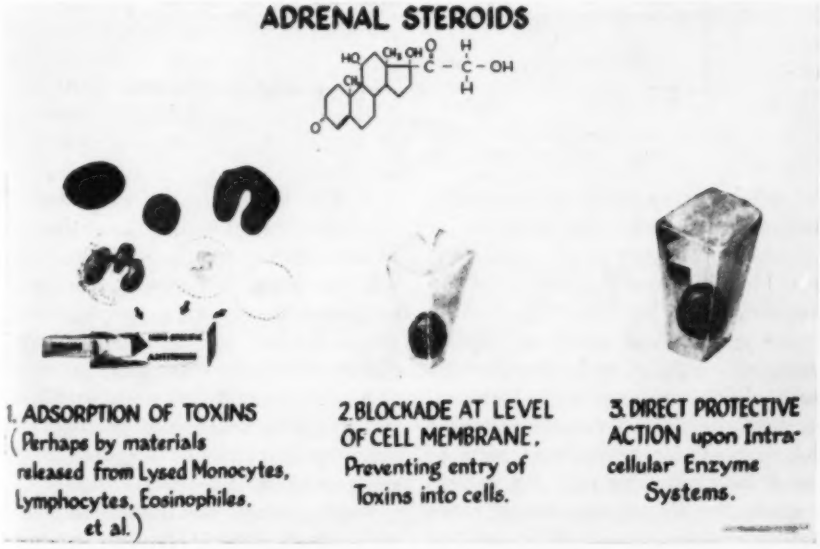
ADRENAL STEROIDS
1. ADSORPTION OF TOXINS (Perhaps by materials released from Lysed Monocytes, Lymphocytes, Eosinophiles, et al.)
2. BLOCKADE AT LEVEL OF CELL MEMBRANE. Preventing entry of Toxins into cells.
3. DIRECT PROTECTIVE ACTION upon Intracellular Enzyme Systems.

Fig. 3.—Three possible mechanisms of antitoxic effects of adrenal steroids.

It is possible that all three effects are exerted on occasion. In addition it has been very amply demonstrated that a major effect of adrenal steroids of the cortisone type is to inhibit the total inflammatory reaction. It is quite possible that a significant portion of the "antitoxic effect" is the result of inhibition of formation and release of products of the inflammatory reaction.

There are very real potential dangers attendant upon the use of ACTH and cortisone in infectious diseases. those patients where there is a very strong probability that death may result before an antibiotic has a chance to take effect; to begin reduction of the hormones as soon as improvement begins; to discontinue cortisone first, ACTH second, and the antibiotics last. It is essential that ACTH be continued for at least a day after cortisone is stopped in order to prevent the possibility of serious adrenal atrophy with consequent collapse after withdrawal of hormonal therapy.

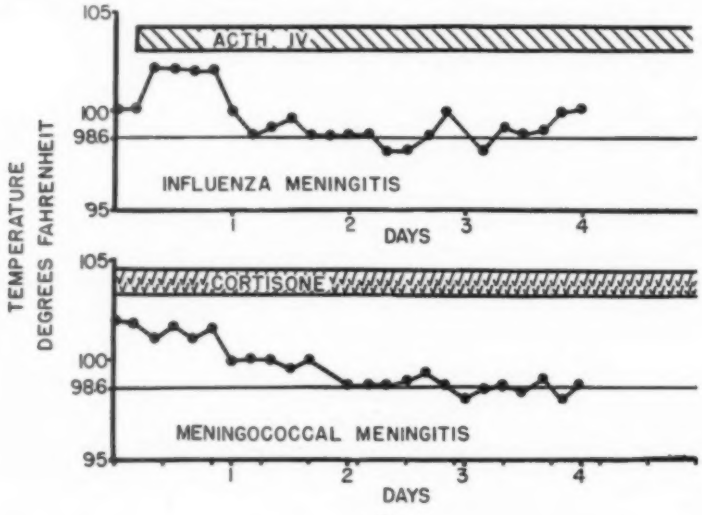

Fig. 4.

The inflammatory reaction is a significant part of the total mechanism of resistance to invading organisms; hence too vigorous inhibition of inflammation per se could conceivably change a localized infection into a widely disseminated one. Further, because of the apparent marked clinical improvement in individuals receiving such hormonal therapy, one may be misled into believing that the patient is much less ill than is actually the case. For these reasons it is essential that one reserve hormonal therapy for

In Fig. 4 is shown the usual response to hormone administration observed in patients with acute infections. You will note that defervescence usually begins very shortly after hormonal therapy is begun. If hormonal therapy is discontinued too soon, that is, before the antibiotic has had an adequate opportunity to fully control the infection, a prompt rise of temperature and reappearance of toxicity ensues.

In the case of meningococcic meningitis per se, during the past two years we have used combined therapy in

twelve such patients, most of whom had proved meningococcemia. Initially it was used only in those patients who were admitted in an almost moribund condition. More recently we have felt that in the case of this disease *only*, one might properly consider routine combined hormonal-antibiotic therapy both on the basis of the results observed and because of the known tendency to adrenal hemorrhage and failure in this disease. Of the twelve patients treated, nine have recovered and three have died. Two of the three died under conditions very similar to those which you have detailed in these two children. These two were treated before intravenous hydrocortisone was available. The third child who died received only cortisone, made an excellent response, and went into sudden collapse and died three days after cortisone was stopped, despite gradual decrease of the hormone. At post mortem the adrenals were found to be quite small.

In closing I would like to suggest a regimen for therapy in patients with meningococcus infection:

1. Institution of intensive antibiotic therapy. Whether this shall be sulfadiazine alone or a combination of sulfadiazine and penicillin is still open to some question.

2. Intravenous administration of a solution containing, in 500 c.c., 25 Gm. of glucose, 1 Gm. of potassium chloride, 100 mg. of hydrocortisone, and 20 units of ACTH. In order to be certain of potency, we use routinely Acthar Gel H.P. The gel dissolves readily in the aqueous solution. An antibiotic may be added to the same solution. Speed of administration must be determined in each case on the basis of individual factors.

3. Tube feeding with a high protein formula is instituted, if at all possible.[1]

4. As soon as improvement begins, oral cortisone is substituted for intravenous hydrocortisone, and intramuscular ACTH for the intravenous material. Ordinarily cortisone is given for a total period of three to four days and ACTH for a total period of four to five days in gradually diminishing amounts.

5. Antibiotic therapy should be continued for at least three days after all hormonal therapy has been discontinued.

6. It is essential to remember that these hormones cause retention of sodium and depletion of potassium; hence intake of these agents must be governed accordingly.[1]

DR. SHAW.—I take it that you do not feel that the principle of cortisone therapy depends upon the concept that adrenal hemorrhage and adrenal failure are responsible for collapse and death in these cases. We have long held that profound saturation with exotoxin is responsible for shock, collapse, cutaneous and adrenal hemorrhages. Is therapy with hydrocortisone effective quite apart from its direct reparative effect on the adrenals?

DR. KINSELL.—That is our belief.

DR. SHAW.—Dr. Kempe, how does this fit with your concept of antibiotic therapy?

DR. C. HENRY KEMPE.—As some of you know, the emergency use of ACTH and cortisone has become standard procedure in the Armed Forces in the treatment of meningococcus disease. We have some misgivings about the combined use of penicillin and sulfa-

diazine in this disease because no one has satisfactorily shown that these organisms are ever resistant to sulfadiazine alone. Conversely it seems not to have been demonstrated that the organism is resistant to penicillin alone although we have seen at least three cases where the patient has failed to respond in a satisfactory manner to penicillin. What there is to be said against the combined use of penicillin is simply that in the past patients have done very well on sulfadiazine alone.

The purpose of using cortisone in acute infection is to attempt to reduce toxicity and to prevent further adrenal cortical damage and thus to combat shock. May not cortisone aggravate the infection by decreasing the host defenses which materially aid the antibiotic to accomplish its end? Along with cortisone therapy a larger amount of sulfonamides or antibiotics may be necessary to overcome this effect of cortisone. There is only experimental support for such a concept but it behooves us to keep it in mind so that when cortisone is employed in fulminant infections it may be advisable to use larger than usual doses of antibiotic drugs.

There has been more meningococcus diseases the last two years, I believe, than in the preceding eight years and the case fatality has also risen out of proportion to the incidence of the disease. This has been noted by Hedrick[2] who has predicted that we are due at about this time for an increase in this infection. Our last epidemic year was 1943 and previous cycles have been at eight- or nine-year periods so that we should be due for an epidemic.

What evidence points to the probability of an epidemic? In the past there has always been a year or two of gradually increasing case rate followed by a year of epidemic proportions. We have had a gradual increase in the past two years in the Armed Forces and in civilian groups so that an epidemic rate might be expected at any time. Since 1943, the last epidemic year, the increased birth rate and the increased flow of population might be expected to increase the number of susceptibles. At the same time, however, the very widespread use of antibiotics may have cut down effective exposure to some extent. The reasons for the increased mortality are somewhat obscure and I do not believe anybody has an answer for this because we are giving as much sulfonamides as usual and there has been no demonstrable increase in resistance of the organism to this drug.

One point particularly emphasized by this second case is the importance of starting therapy promptly when the diagnosis is made regardless of when hospital admission takes place. The diagnosis can frequently be established beyond doubt on purely clinical grounds and sulfonamides should immediately be given before the patient is sent to the hospital. The delay of an hour or two in treatment may be the difference between survival or death. The use of intramuscular Gantrisin may offer a simple measure for the introduction of sulfonamides into the patient with small and collapsed veins who cannot take or retain things by mouth.

DR. SHAW.—You did not mention, Dr. Kempe, the fact that experimentally some meningococcal strains have been facultated to penicillin as a necessity for growth. It is a curious thing that more than one antibacterial

agent is so frequently employed when a single one, the sulfonamides, is so very effective.

DR. KEMPE.—Dr. Jawetz has perhaps done the best original work on combined therapy and has pretty well convinced me that two agents may frequently be worse than one alone. How much this applies to clinical problems no one really knows but all of us must have seen some instances where the patient has seemed to have done better when several antibiotics were withdrawn in favor of one or two which were proved to be effective. In meningococcal disease I still favor the use of a sulfonamide with such other supportive therapy as Dr. Kinsell has indicated.

DR. SHAW.—By and large there is a good deal of urgency to do all you can do and to do it quickly. Most cases of fulminant meningococcemia get two or three therapeutic agents before they are through. I believe we are better off with a single agent which we know to be effective. Failure in the treatment of these cases is mostly that we run out of time and the patient succumbs before therapy has had an adequate opportunity.

Unfortunate end results in the treatment of purulent meningitis are sometimes seen in those who survive the acute illness. The next two cases will illustrate this point.

DR. LEVIN.—Our third case this morning was admitted to this hospital a month after the onset of meningococcus meningitis. This patient had been violently ill for a number of days before she was seen by Dr. Herbert Herzon of Pittsburgh who promptly established the diagnosis and instituted intensive therapy when the child was practically moribund. She gradually rallied under treatment and was admitted to our care four weeks after onset. At this time this 7-month-old baby showed extreme irritability with constant crying. She was indifferent to everything about her. She would follow her bottle with her eyes but sucked quite poorly. Her neck and back muscles were flaccid and she made no attempt to sit or to hold up her head. The fontanel was small and not bulging and there was no change in percussion note over the skull. The eye grounds were normal.

Spinal puncture showed a fluid with 41 white cells per cubic millimeter, 27 polymorphonuclears, 14 monocytes, and sugar of 47 mg. per cent. During her hospital stay she made but little improvement. She continued to be extremely irritable but she began to notice people about her and to follow them with her eyes. She was still unable to sit or to hold up her head and there was moderate spasticity in all four extremities. Clinical studies and the later performance of air encephalograms established the diagnosis of extensive adhesive arachnoiditis as the cause of her symptomatology and satisfactorily excluded subdural hydroma, abscess, or other surgically accessible lesions as the cause of symptoms. The child was finally dismissed with a diagnosis of severe cerebral damage as the result of long-standing meningitis prior to treatment.

Our fourth case is one of *H. influenzae* meningitis which has been followed here for the last seven months. This 3½-year-old boy began his illness with anorexia, vomiting, lethargy, and fever during the early morning prior to admission. He apparently had a mild convulsion about 3 A.M. He was

admitted to the hospital early in the morning, at which time he had neck stiffness, positive Kernig and Brudzinski signs, and hyperactive tendon reflexes. The spinal fluid showed 6,700 cells per cubic millimeter, almost entirely polymorphonuclears; the spinal fluid sugar was 18 mg. per cent. Cultures showed *H. influenzae* type B. Therapy was immediately started with parenteral sulfadiazine and streptomycin. By the end of the first hospital day he was afebril but still comatose. His temperature rose during the second hospital day and on the third day he had repeated convulsions in spite of numerous anticonvulsant measures. On the fourth day spinal puncture was repeated; the fluid showed 200 cells with no organisms on smear or culture. On the fifth day streptomycin was discontinued, sulfadiazine was continued, and he was started on generous doses of Chloromycetin. He continued to be very apathetic but was afebrile. On the seventh hospital day his spinal fluid showed 9 cells per cubic millimeter with normal findings otherwise. By the twelfth day he was believed to have recovered completely from meningeal infection but was profoundly apathetic and it was impossible to elicit any response from him to visual, auditory, or even painful stimuli.

During the third week of his illness there was gradual improvement in his status, he became less apathetic, and showed some response to auditory stimuli which relieved our fears that the damage might be due to streptomycin. It finally became apparent that he was improving in every way except for his vision, and at the time he was dismissed from the hospital he seemed to be completely blind.

Since dismissal he has been followed by Dr. Shaw who can report his further progress.

DR. SHAW.—Since dismissal from the hospital this boy has shown steady improvement. From his original state of complete apathy, almost coma, he has gradually roused and has been finally able to recognize voices, to carry on conversations, and finally to be pretty much his normal self except that he was completely blind. He lost his ocular reflexes and his pupils were widely dilated. The fundi were readily visualized and always appeared normal. The first evidence of improvement in his visual apparatus was the return of his pupillary reflexes and he has shown a gradual improvement in vision until now as I present him to you I think I can demonstrate that he sees although he does not see well. You will observe that he obviously distinguishes a bright light and as he walks about the room is able to recognize obstacles in his path, but he still does not recognize faces or discriminate very much about objects in his vicinity. You will observe that he definitely hears well, he recognizes my voice and answers my questions, he moves around fairly adeptly, and uses all four extremities well. There has been so much improvement successively in his various motor and sensory functions that I am encouraged in the belief that his visual acuity will also gradually return. He has been seen by a number of consultants including Dr. Faber who is here to discuss him this morning. Air encephalograms have been proposed by one consultant but there has been some reluctance on the part of the parents to have these carried out. I have personally been

opposed to air studies in the belief that a space-consuming lesion such as a subdural hydroma was an unlikely cause for his diffuse symptoms and one can hardly blame the parents for being unwilling to accept a more or less dangerous procedure at a time when his general progress was upward. I am disinclined to be too optimistic but if one can project his rate of improvement into the future, complete recovery would not seem too unlikely. Dr. Faber, will you give us your opinion.

Dr. Harold K. Faber.—The patient is considerably better than I would have expected when I saw him about three months ago. At that time he was completely disoriented and obviously had a very severe encephalopathy. We are, I think, inclined to regard bacterial meningitis as a purely superficial infection of the meninges. In a fair percentage of cases definite encephalitis is associated with this infection. Dr. Alexander, in her series of sixty-five cases of *H. influenzae* meningitis, records six such complications. In sixty-one recovered patients four were very seriously and permanently damaged and another two had less severe but marked residuals, making the total instance of this form of encephalopathy about 10 per cent. Alexander ascribes this to arteritis with resulting anoxia and destruction of brain cells. Apparently venous thrombosis also occurs sometimes in cases of this sort. With the very much higher percentage of recovery which we are now getting, many patients would have died before we had effective therapy and some of these now survive only to suffer from permanent sequelae. I do not know how much better results we can anticipate even with the best treatment now available. I am particularly pleased with this patient's considerable degree of recovery which is greater than I had expected and which is decidedly encouraging. In regard to air studies, I agree with you that unless there are definite signs of increased intracranial pressure they are not indicated and even then can sometimes be avoided by subdural taps because the main objective is to discover the presence or absence of subdural accumulation of fluid.

Dr. Shaw.—Dr. Henry, would you like to say a word about this boy even though you have not had a chance to examine him? I might add that among the agents used in treatment was the administration of nicotinic acid in sufficient dosage to give him definite facial flushing. This did not seem to result in coincident improvement of his vision.

Dr. Margaret Henry.—Amaurosis or blindness as a result of meningococcic meningitis has been described. This is the first case that I have noted in which the child was left visually handicapped without ophthalmoscopic changes. It is thought in those cases that it is either due to optic neuritis or that the blindness is cortical. Walsh in his textbook states that they usually do improve although some cases have been reported with severe loss of vision. This case would have to be followed. If the lesion is in front of the geniculo-calcarine pathway he should eventually show atrophy of the ocular nervehead.

The most frequent ocular complication of meningococcic meningitis is iritis and endophthalmitis or panophthalmitis. Another frequent ocular complication is strabismus or some ocu-

lar paresis. Of course, they may have nystagmus or pupillary changes. Meningococcic conjunctivitis may be the initial symptom or may occur as a complication of the systemic infection.

It is my opinion that this child had a severe transverse interstitial optic neuritis sufficiently far posteriorly to allow the nervehead to appear normal.

When optic neuritis is present the pupils are dilated and fixed to light. Where the blindness is cortical the pupillary reactions remain normal. His pupils now react to light?

DR. SHAW.—Yes.

DR. HENRY.—At first they did not?

DR. SHAW.—No, they did not.

DR. HENRY.—The pupils were fixed and dilated. We will just have to follow him. It would be of value to do optic fields but he is only 3½ years old?

DR. LEVIN.—He does not have much in the way of fields now.

DR. HENRY.—These might help us either to localize the damage and to give us additional information a little later on.

DR. SHAW.—Dr. Finley, you read the encephalograms on this boy. Have you any comments?

DR. KNOX FINLEY.—The EEG is about what one would expect. There is a diffuse change with shifting foci from one hemisphere to the other. This is not an uncommon finding in the EEG as a residual of meningitis. I should like to make a comment concerning the neuropathology of meningitis. Whenever one has an inflammatory lesion within the subarachnoid space, particularly an acute fulminating one, there will always be a reaction in the subpial area or first layer of the cerebral cortex. This will result in a reaction on the part of the astrocytes and possibly the microglia and there may or may not be some extension of paravascular lymphocytic infiltration extending in from the subarachnoid spaces. As the first zone of the cerebral cortex is one of the primary association zones for all the underlying five layers of the cerebral cortex, it is not surprising that we find associated with meningitis a varying degree of disorientation and confusion. It is not necessary therefore to assume a cerebral arteritis to account for this clinical confusion and disorientation. From my experience any arteritis in acute meningitis sufficient to impair the circulation to the cerebral cortex does not occur. Such an arteritis may occur, however, in some of the more chronic meningitides such as tuberculosis and syphilitic meningitis.

Dr. SHAW.—Dr. Adams, both of these late cases have neurosurgical implications. Will you give us your comments?

DR. JOHN ADAMS.—I do not believe that any of these four patients present a surgical problem at the moment. The surgical approach to the complications of meningitis is a fairly obvious one. A surgical problem presents itself when in the acute stages of the disease the patient is combating markedly increased intracranial pressure whether it be due to subdural accumulation of purulent material or to an area of focal encephalitis which is later on going to break down and become an abscess. With present-day antibiotic therapy one is justified, I think, in interfering a little earlier than we used to do if increased pressure threat-

ens life more than does the infection itself. Formerly we have always waited until an abscess had localized either intracerebrally or in the subdural space and then drained it. Today if one has an acute problem in a child or adult who shows evidences of increased pressure and is in danger of losing his life from this pressure and at the same time shows evidence of focal disease, one can, as a lifesaving procedure and with the help of antibiotic therapy, actually remove the area of encephalitis. If there is sufficient accumulation of pus, needle drainage can be done as a lifesaving procedure, and later on when the patient is improving, the abscess can be removed surgically.

I would like to make one comment about this last boy. I agree from the standpoint of the youngster himself that air studies would probably not prove anything and would not add anything in the way of prognosis or of understanding of the problem. Nevertheless, I think they would be interesting from a purely academic standpoint. It seems likely to me that this boy has some thrombosis or vascular involvement of drainage of the deeper area of his brain, especially of the diencephalon, which may explain his marked degree of mental changes, his unawareness and confusion, although, as Dr. Finley has stated, cortical disturbances could afford this explanation. It seems to me that one thing that could tie together his loss of vision with his prolonged alteration in consciousness would be interference in venous drainage by thrombosis of vessels draining the diencephalon. I agree that arterial involvement probably does not occur in the meningitides but certainly venous thrombosis does.

DR. SHAW.—I would like to ask Dr. Adams for his comments about the third case in which there was extensive destructive change with adhesive arachnoiditis. Three of the patients presented were treated early and with agents which should have been effective. This one case represents the failure in a patient treated at a late date in which the child barely survived only to have this dismal end result.

DR. ADAMS.—Do you know if she had any intrathecal medication?

DR. SHAW.—No, she did not.

DR. ADAMS.—I take it from your question that in the first place you would like to know if anything further could be done now and I think the answer to that is no because the effect on the parenchyma of either the brain or the cord secondary to adhesive arachnoiditis is primarily vascular. The vessels which supply the parenchyma are probably gradually obliterated by the adhesive process, the tissue suffers from progressive anoxia and dies. Such a process is sometimes the result of intrathecal medication and my neurosurgical experience prejudices me against this form of treatment. When such a process is confined to the spinal cord something may be gained by laminectomy and the removal of as much of the adhesive process as possible. By so doing one gets rid of the so-called waterhammer effect where the cerebrospinal fluid in its circulation about the cord pulsates with the pulse and respirations and exerts extreme pressure at the site of obstruction. If this water hammer effect can be eliminated by the removal of obstructing adhesions there may be subsequent improvement. I know of no way to prevent arachnoiditis in meningitis except

by the avoidance of intrathecal medication unless this seems to be absolutely necessary.

DR. SHAW.—Would you draw any parallel between the third and fourth cases?

DR. ADAMS.—No. I think that in the third case bad results were due to adhesive arachnoiditis and that this can fairly well be eliminated as a possibility in the fourth case. I believe the child with *H. influenzae* meningitis had no such sequela and that his symptoms are due either to thrombosis or to a complicating encephalitis or cerebritis.

DR. H. E. THELANDER.—I would like to recur to Dr. Kinsell's discussion to ask if it is proper to regard cortisone or ACTH as purely antitoxic. I would be reluctant to think that meningococcus exotoxin could be neutralized with cortisone. There is an extreme concentration of toxin in some cases of meningococcemia. The organisms teem in the circulation and can frequently be picked up on direct blood smear. I wonder if cortisone can exert antitoxic powers adequate for this situation. If one can compare this disease with diphtheria, Dr. Kinsell, would you dare thus to treat a toxic diphtheria?

DR. KINSELL.—I would like again to emphasize that we have used the term "antitoxin" as one of convenience. In a clinical sense, the effect is definitely one which can properly be called antitoxic. We are very certain, on the basis of extensive animal and human data in the literature, that however the effect is produced, there is no increased production of any *specific* antitoxic material. In the case of exotoxins, such as diphtheria and tetanus, most of the data currently available indicate that there is little or no protection conferred by adrenal steroids. In a recent interesting paper from the Pasteur Institute, called to our attention by Dr. Jawetz, it would appear that there is significant protection conferred against certain endotoxins.[3]

DR. SHAW.—I believe that the child who was treated so late in her disease and wound up with adhesive arachnoiditis received cortisone during her period of heroic—but late—treatment and that this was given in accordance with Dr. Hodes' recent advice. Is it possible that cortisone so used contributed to her immediate recovery but may also have contributed to the serious fibrotic end result?

DR. KINSELL.—To the best of my knowledge, there is nothing which would suggest that ACTH or cortisone is contraindicated in patients with late inflammatory or fibrotic changes resulting from encephalitis. In one patient recently we have administered large amounts of hormones in the hope that some "fibrolysis" might result. On the other hand, we feel very strongly that in the presence of acute viral infections for which antibiotics are not available that, for the present, hormonal therapy must be considered contraindicated because of the danger of dissemination of the infection. The one exception which we would make to this on the basis of considerable experience during the past three years is severe viral hepatitis which appears to be progressing to a fatal termination.

DR. LEVIN.—Would you comment, Dr. Kinsell, on the use of adrenocortical extract in emergency situations such as in the first two cases?

DR. KINSELL.—It can be used if you use gallons of it, but if the intravenous hydrocortisone is not available, intravenous ACTH is the drug of choice and should be used rather than the adrenocortical extract.

DR. SHAW.—A patient was admitted yesterday by Dr. Baumann which illustrates emergency measures in these fulminant cases and this will initiate our discussion next week.

SECTION II

DR. SHAW.—The case referred to in our last session will be reported by Dr. Pearson.

DR. DELBERT PEARSON.—This 2-year-old boy was admitted to the hospital after being ill for about twenty-four hours. At 3 A.M. the parents noted a petechial eruption over the extremities. He continued to be drowsy and ill during the day but was not seen by a physician until twelve hours after onset. At 3 P.M. he was brought in to Dr. Baumann who promptly recognized the condition and believed that he would hardly survive long enough to reach the hospital. He gave the child 1,200,000 units of penicillin, 2 Gm. of Gantrisin intravenously, and 20 units of lipo-adrenal, which was the only immediately available product of this kind, and forthwith sent him to the hospital. He arrived at the hospital one-half hour later in desperately bad condition. He was promptly started on intravenous hydrocortisone, receiving 100 mg. during the first twenty-four hours which was repeated during the second twenty-four hours along with 100 mg. of cortisone intramuscularly. Sodium sulfadiazine in a dosage of 1½ Gm. for twenty-four hours was given subcutaneously, being started immediately.

The blood culture was negative. Spinal fluid showed 2,400 cells with 98 per cent polymorphonuclears and the fluid showed many meningococci on smear and culture.

The response was dramatic. Within eight hours his temperature dropped to 38° C. (R) and remained below this point for his entire hospital course. During the next few hours his color and general appearance rapidly improved and by the morning after admission he was moving around and was much more responsive. Toward evening of this day he cried a lot, seemed to be in great pain and was given a small dose of codeine. During the next two hours he was very lethargic and developed cardiac arrhythmia. The electrocardiogram showed a shift from nodal to sinus rhythm with some changes compatible with mild carditis. The T waves were normal, however, so that there seemed to be no electrolyte problem. The following morning without any especial change in therapy he was greatly improved and the remainder of his course was relatively uncomplicated.

Hydrocortisone was discontinued after forty-eight hours of slow continuous intravenous drip of 100 mg. daily. Intramuscular cortisone was given 100 mg. daily for two days, 50 mg. the third day, 25 mg. the fourth, and on the fourth day he was given 80 units of ACTH and another 80 units on the following day. At dismissal he seemed to be entirely recovered in every way.

DR. FRANZ BAUMANN.—I feel that without hydrocortisone this child could not possibly have survived. When seen in my office he was in complete collapse and his pulse and blood pres-

sure were unobtainable. That his blood culture was negative on entry was probably due to the intravenous Gantrisin which seems like a good antibacterial drug for such emergencies. The final use of ACTH was for the purpose of stimulating his own adrenal function.

DR. SHAW.—I believe this child's life was saved only by prompt action on the part of Dr. Baumann and by the fortunate use of hydrocortisone after arrival at the hospital. I have only seen similarly dramatic results with the use of potent antitoxic serum. Only an agent which can black the tremendous intoxication in such a patient will afford us a sufficient interval for effective treatment with sulfadiazine or antibiotics. The presently available agents all require an appreciable period of survival before this treatment can be effective and this is true of ordinary cortisone. On theoretical grounds ACTH would seem less likely to be effective than hydrocortisone in such a severe situation.

* * * *

We will now proceed with the consideration of a small group of virus infections of the central nervous system which are of especial importance to us because they occur at about the same time as epidemics of poliomyelitis, and their symptomatology somewhat mimics that disease. Dr. Levin will summarize the few cases of Western encephalomyelitis and St. Louis encephalomyelitis which we have encountered during the last two months.

DR. LEVIN.—I shall briefly summarize our six cases of the insect-borne encephalitides. These few cases all occurred during a few weeks' period in July and August, 1952.

Our two youngest and most severely ill patients were boys 2 and 3 months old, both from Chico. In one case it was known that a horse died on a neighboring farm of encephalitis. In the other, there was no known history of the disease in horses but the infant had had numerous mosquito bites. Both children were admitted with a chief complaint of fever and convulsions. Neither showed meningeal signs on admission. One seemed very much out of contact and stuporous. Lumbar punctures done before entry revealed lymphocytic pleocytosis. The infants ran a febrile course for five and seven days, during which time they had frequent convulsions and hyperactive reflexes. These signs decreased when their temperatures returned to normal. Both developed meningeal irritative signs during their hospital stay. The diagnosis of Western equine encephalitis was confirmed in each by serological studies.

The 2-month-old infant was readmitted six months later when he began to crawl and it was noted that he did not use his right arm and leg as well as the left ones. On this admission he was found to have definite spasticity of his right side.

The next patient is a 4-year-old white male admitted with a chief complaint of fever and drowsiness from an area where there was known encephalitis. He had marked meningeal signs during his four-day febrile course which cleared when his temperature returned to normal. A rising serologic titer to W.E.E. was demonstrated.

A 6-year-old girl was admitted with fever and stiffness of eight hours' duration. She was ill only two days in all and the meningeal signs rapidly

improved. The diagnosis of Western equine encephalitis was later made by serologic studies.

A 19-year-old farm laborer was admitted with marked tremulousness, fever, and stiffness. He remained febrile for several days. His meningeal signs and fever cleared although he left the hospital early and not completely recovered. Two blood specimens taken close together showed a definite rise in titer for Western equine encephalitis.

Another patient was a 36-year-old man admitted from Corning for post-polio care. The patient was well until July 27 when he developed neck and back stiffness and leg weakness. He was hospitalized in Corning and received conventional polio care. On his arrival here he had minimal neck and back stiffness and diffuse symmetrical lower extremity weakness with brisk tendon reflexes—certainly atypical for poliomyelitis. A convalescent specimen of serum was sent to the State Laboratory which showed a positive titer for St. Louis encephalitis 1:64. There was some question whether this was an anamnestic rise during polio or was indicative of St. Louis encephalitis as the primary disease.

DR. SHAW.—I now wish to introduce Dr. Longsshore and Dr. Kokernot of the State Department of Health who can summarize for us the state situation with respect to encephalomyelitis during the last few months.

DR. WILLIAM ALLEN LONGSHORE, JR.: A brief résumé of some of the highlights concerning encephalomyelitis from previous experience in California related to the cases which have been presented might give some picture of the problem outside of the hospital and in the community at large. The problem of encephalitis in this state has been recognized since 1932 when Dr. K. F. Meyer of the Hooper Foundation postulated that if Western equine virus could make horses sick there was no reason why human beings could not be made ill by the same virus. It was not until 1938 that Western equine virus was isolated from a fatal human case. St. Louis encephalomyelitis was recognized in 1939 and isolated in 1945. About 1945 laboratory tests became available and fairly intensive case findings was initiated, especially in the Kern County area, by the Hooper Foundation and the State Health Department. Totals of 302 (1945) to as low as 71 (1948) have been reported. In 1950 we had a considerably large outbreak of some 357 reported cases and last year we outdid ourselves with 805 cases reported throughout the state.

Laboratory diagnoses were obtained on as many cases as possible, and in 414 of these, 370 proved to be Western equine encephalomyelitis and 44 were due to St. Louis virus. These diagnoses depended on examinations of acute and convalescent blood specimens usually taken ten to fourteen days apart. In 189 blood specimens submitted from patients clinically suspicious, serological tests were negative for Western equine, St. Louis, and mumps. There were 104 such cases with inconclusive laboratory tests. One patient was mentioned today in which a single blood specimen was obtained but which showed a significantly high titer. The question always arises in such instances whether the patient had had experience with the disease to account for his increased

serologic titer or if this is the result of the illness under observation. I have no information regarding the possibility of an anamnestic phenomenon affecting Western and St. Louis complement fixation or neutralization tests in response to other infections which these patients may acquire. We hope that by taking bloods from patients with encephalitis, following up these patients and observing and testing them during intercurrent illness we can determine something about anamnestic responses in these two viruses. At the moment I know of no evidence to substantiate this interesting theory.

Concerning the geographic distribution of the disease: In the past, forty-six of the fifty-eight counties in California have reported the clinical syndrome and this year forty-one counties reported cases, but in only twenty-three of these counties were we able to get laboratory confirmation. This follows the pattern of previous years in that the disease as represented by the laboratory-confirmed cases has a fairly rigid and well-defined area of occurrence which is predominantly in the Central Valley counties with Western and St. Louis virus showing essentially the same distributions in the state. The coastal and mountain counties are usually unaffected. The highest case rate came from the lower San Joaquin Valley: Kern County 222, Fresno County 138, San Joaquin 92, Sacramento County 65, Stanislaus County 42, Tulare County 44, and in a few other localities in smaller numbers. The highest attack rate based on the 1950 census occurred in Kern County with a rate of 97 per hundred thousand. The second highest was Sutter County with 61 per hundred thousand.

Our information on horses is inadequate but we do have information that there were some 400 horse cases this year. In 1933 to 1936 some 5,000 or 6,000 would get the disease annually and about 50 per cent would die. One thing which disturbs us is that although few human cases occur outside the valley area, nevertheless horse cases are commonly encountered in other areas, proving that the infection is present and raising the interesting question of why it is not transmitted to human beings as it is in the Central Valley.

The five cases mentioned here this morning all occurred in July or August and this seasonal occurrence is typical for the entire state. Cases of clinical encephalitis are reported the year round, the peak for human beings being in July and falling off steadily through October, but we do not obtain laboratory confirmation of either of these infectious agents prior to June or after October. Even though the syndrome is reliably reported and appropriate blood specimens are obtained, we are unable to show antibody rise outside of this restricted season. This may be related to the prevalence of the *Culex tarsalis* mosquito which is believed to transmit the disease and is more prevalent during these months, and during this time the prevailing high temperatures in the Central Valley may encourage the development of the virus in the mosquito.

Another point worth noting is a distinction between Western and St. Louis viruses in seasonal occurrence. Western virus appears in June; St. Louis virus appears a month later and normally supplies most of the cases which occur in August, September, and October, during which later months the

Western virus drops out. We do not know what produces this difference in seasonal activity, it seems to be very definite and it has occurred year after year. This year was unusual in that of the total number of confirmed cases of St. Louis virus constituted only forty-four out of 414. Whether reduced incidence of St. Louis cases followed extensive emergency mosquito control measures means that this effort was successful is not clear. An interesting fact is that the forty-four cases which did occur is the second highest number of St. Louis cases ever experienced in this state, so that if you compare St. Louis cases with other years there was an adequate number, but if you compare it in proportion to the Western cases it fell far short of what would be expected.

Age and sex show some very interesting data. In 1952 26 per cent of the total reported cases were under 1 year of age and 39 per cent under 10 years of age. There were not enough confirmed St. Louis cases to break down. In our consideration of Western equine cases we find that 25 per cent were under 5 months of age, 29 per cent under 1 year, and about 50 per cent under 10 years of age, thus comprising a considerable pediatric diagnostic problem. This age distribution is typical of our experience with Western virus. St. Louis encephalitis is quite different and rarely occurs under the age of 1 year. During a ten-year period there have been only three out of 200 confirmed cases of St. Louis virus which occurred in this age group. This discrepancy in behavior of the viruses is difficult to explain. If you have a patient under 1 year of age with either of the two arthropod-borne encephalitides you can say with relative security that it is Western equine encephalomyelitis and not St. Louis virus.

Occupation may be related to the sex differential. Males predominate about two to one. Occupational exposure may be a plausible explanation for this distribution in older patients but it is difficult to apply this explanation to age groups of 5 to 9 years where the same sex difference still applies. The parents' occupation might help to explain this finding and we are attempting to get more details on this point.

With respect to rural and urban distribution, the impression has been that rural areas have a much higher rate than cities and it has been stated that this is due to differences in exposure to mosquitoes.

In addition to the above epidemiological facts there are several interesting points worth comment. We found fairly good evidences of intrauterine transmission of Western equine virus. This occurred in 7-day-old twins who were delivered in the hospital, went home for twenty-four hours, became clinically ill and were readmitted to the hospital. Both showed rising titers to Western equine virus. Detailed investigations supported the probability of intrauterine transmission.

This year is the first time that a sufficient number of positive serologic studies has made it possible to examine the validity of the various tests. The complement fixation test appeared to give very good results while neutralization tests seem to be less satisfactory. One of the disturbing features was the fact that physicians in our hospitals and epidemiologists in the field were finding cases that were clinically encephalitis but blood specimens were negative for both Western and St.

Louis virus and for mumps (which latter infection might be confusing clinically). The arbitrary interval of ten to fourteen days between the collection of acute and convalescent blood specimens was questioned. It was considered that some of these individuals were not producing antibodies as rapidly as had been expected and that they should be tested for an interval of a month or so. When this was done about 10 per cent of the cases in the Kern County area became positive in tests of the third blood specimen. This variation applied only to the older age group, children always showing significant rise in titer in ten to fourteen days if this rise appeared at any time. Older individuals seemed not to produce complement fixing antibodies as rapidly as infants.

A problem of great importance is to determine the cause of the 25 per cent of clinical cases of encephalitis who have negative serologic tests for Western, St. Louis, and mumps virus. Are they "California virus"? Are they nonparalytic poliomyelitis? Coccidioides? Are they of undetermined and unrecognized virus etiology? We are very much interested in this problem and this is one reason why we have attempted to obtain autopsy specimens on all fatal cases in the hope that a new viral agent might be isolated. We have been unsuccessful. All of the negative blood specimens from patients with clinical encephalitis have been tested for Japanese B, Eastern equine, California virus, and the virus of lymphocytic choriomeningitis with consistently negative results. We have attempted a follow-up study of the patients with positive serologic tests. In two of the cases presented today there were residual effects. Our impression has been that only 1 to 2 per cent of patients suffering from acute encephalitis, excluding the 5 to 6 per cent who die, will show residual effects and will recover completely. These statements require factual support so that our study has been devised to determine the frequency of these residuals, their range of severity, and their time of appearance. We have been able to follow about 250 of those definitely diagnosed serologically with later neurological studies. A grant has been applied for and we hope to continue this work from five to ten years.

We are also following blood titers in these late cases so that we can finally determine the persistence of antibodies and evaluate the significance of single specimens with titers as high as 1 to 64, etc.

The question of the immunity status of the population is to be further studied. We have been considering the use of a skin test similar to that employed in mumps so that we may judge the susceptibility rate in a given area. The possible use of vaccine has also received consideration. If there are a sufficient number of susceptibles and a suitable vaccine can be devised, this might be employed along with mosquito control to reduce the case rate in major epidemic areas. There is a vaccine for horses and with some precautions this can be used in human beings with a successful production of antibodies. We have employed this material to some extent for individuals who are at very high risk.

DR. SHAW.—Our particular problem is that most of these patients with central nervous system virus disease are sent in to us as polio and along

with these are a number in which the suspicion of polio is not very great. In a considerable percentage we can quickly establish an alternative diagnosis. Those with definite central nervous system disease can sometimes be screened very quickly to determine that some are definite encephalitis and some are definite polio. Those with very high fever, convulsions, and disorientation are not likely to be polio. Our greatest trouble comes in the intermediate group, those in which symptoms are very mild and the patient comes in with some fever, a little neck stiffness, and variable spinal fluid findings. Some patients have to be accepted as nonparalytic polio simply by our failure to establish any alternative diagnosis by any test which we can apply. Some are more meningitic and many of these turn out to be mumps. Once in a while we are disturbed by the patient who almost coincidentally has mumps together with definite paralytic polio. We have had at least two such that I can recall quickly. We always look for benign lymphocytic choriomeningitis in late blood studies but have never been able to establish this diagnosis by laboratory tests. Have you, Dr. Longshore?

DR. LONGSHORE.—There has been only one in the state during the last ten years.

DR. SHAW.—Almost everything diagnosed clinically as benign lymphocytic choriomeningitis turns out to be either mumps or nothing much of anything. There must be other viruses which complicate this picture. There is a pseudochoriomeningitis and maybe there is a "pseudopseudo."

Too ready acceptance of the diagnosis of nonparalytic polio will provide a wastebasket for every sort of summer illness. It has been suggested that in the polio season diagnosis of nonparalytic polio may rest upon sore throat, headache, vomiting, nausea, fever of otherwise unexplainable origin, with or without positive spinal fluid findings. Casual acceptance of the diagnosis of nonparalytic polio may push our reporting of the disease to astronomical figures. Our own experience has been that if the early diagnosis of poliomyelitis is based only on evidence which is clinically quite convincing that only a small percentage will escape paralysis which is detectable either early or late. During the past year we had approximately 290 patients with polio and in these there were only twenty in which the final diagnosis was nonparalytic polio—approximately 7 per cent—and among these there were only four in which we were completely confident of the diagnosis, the remainder being finally diagnosed mostly on the basis of our inability to establish an alternative diagnosis.

The question of what to accept as poliomyelitis is of more than academic interest—it is of vital importance to insurance companies who underwrite polio policies and to charitable organizations who assist in the care of these patients. Fortunately nonparalytic cases require only a short period of care.

The detection of minor weakness demands only a simple routine of ex-

DR. LEVIN.—This child came in last October with a fairly typical history of influenza-like symptoms, fever, stiff neck, and stiff back. The admission spinal fluid showed 138 cells per cubic millimeter, 61 per cent polymorphonuclears. Initially he was very tremu-

lous and ill and seemed like a typical and moderately severe polio. Exhaustive tests of muscle strength were not made in the early acute stage and he was dismissed as nonparalytic polio after he had been afebrile for a week. The existence of muscle weakness was only demonstrated in careful follow-up examination.

DR. SHAW.—The physical therapists do very meticulous muscle examinations on these patients. The clinician of ordinary experience can make a rapid examination which will reveal muscle weakness with surprising accuracy if he will only observe carefully.

This patient does not cooperate very well at this moment but I believe I can show you this two-minute muscle check. First have the patient lie down, hold his knees on the table, have him fold his arms, and sit up. You will notice that this child wriggles to a sitting position, and if you watch his umbilicus you will note that it shifts to the left because the abdominal muscles are weaker on the right. Then sit him on the edge of the bed with his head pressed against the examiner's chest. The patient grasps my hands and then against some resistance attempts to pull my hands apart and then to pull them together while I carefully watch down his back for any winging of the scapula or scoliosis of the spine. Shoulder girdle weakness is very likely to be bilateral so that at one time you will think it is on one side and then again on the other. After careful inspection of the back to detect weakness or stiffness on one side or the other, the patient is now allowed to stand. One foot is now held off the floor and he is encouraged to rise on one tiptoe and then to rock back on his heel and raise his toes from the floor and then to execute a full squat on the single extremity. This is now repeated with the other lower extremity. I think you can note even at some distance that this patient does not execute a situp with normal strength and balance and that inability to rise firmly on his right heel indicates definite—although mild—weakness of the anterior tibial on this side. This weakness can also be observed as he now walks across the floor.

This child may go on to complete recovery from this point on but his mild abdominal weakness may lead to trunk imbalance and a scoliosis which once started may be progressive. The very mild weakness in the anterior tibialis with overuse of his great toe extensor may gradually lead to contracted plantar fascia and finally a deformed and awkward foot. It is of much more than academic importance to detect these mild degrees of weakness for they point to residuals in which late deformity and disability is completely preventable. Among our patients with definite polio only a few escape weakness which is easily observed and among these few the majority will show slight degrees of weakness which may be detected by systematic follow-up examination.

I see there are some questions from the floor about our general topics.

DR. FRANZ BAUMANN.—I would like to know how long the immunity in horses persists after vaccine injection.

DR. LONGSHORE.—It usually lasts at least twelve months and perhaps longer but yearly injections are the rule in epidemic areas.

DR. BAUMANN.—How high do the titers go and how soon?

DR. LONGSHORE.—An adequately protective titer usually results in seven to ten days.

DR. SHAW.—Can patients be protected from the mosquito by the same dose of thiamine which will repel fleas?

DR. LONGSHORE.—Mosquito repellents are of some value but the amount of B_1 which would need to be employed in the Central Valley in summertime would make the producers very happy.

DR. SHAW.—It might not be so colossal as compared to the amount of vitamin preparations which are sold!

DR. EUGENIA HERRON.—Is the immunity in human beings permanent?

DR. LONGSHORE.—So far as we know there is lasting immunity for we have had no patient who has had the disease previously. We have had double infections but I know of no case where the same infection occurred more than once in the same individual. There seems to be no cross protection between St. Louis and Western virus.

DR. BAUMANN.—What was the mortality in this last year's epidemic?

DR. LONGSHORE.—About 6 per cent of the clinically recognized cases.

DR. BAUMANN.—Do the older or the younger age groups seem to be more susceptible and how does the severity of illness compare with respect to age?

DR. R. H. KOKERNOT.—Susceptibility is apparently greater in the younger age groups as quoted by the figures of Dr. Longshore. Fifty per cent of the encephalitides of known etiology occurred under the age of 10 years. There is wide range in the clinical picture with little difference in the severity at different ages. Some of the infections of older individuals were complicated by cardiac conditions and other intercurrent complications to increase the over-all severity.

DR. LEVIN.—Can you discriminate clinically between St. Louis and W. E. E.?

DR. KOKERNOT.—No, only in the laboratory. However, when the differences in seasonal occurrence and age distribution are considered, there is some clue to the differentiation.

DR. SHAW.—Over the years I have thought that the patient whose clinical picture resembled typhoid, who was feverish, surly, and moderately stuporous, and who proved to have a spinal fluid pleocytosis was more likely to have St. Louis encephalitis than Western equine. Certainly this is based on meager observation.

DR. KOKERNOT.—This has not been our general observation.

DR. LEVIN.—Among our cases this year convulsions occurred only in the two small infants. Do convulsions occur only in infancy?

DR. KOKERNOT.—Yes, fever and convulsions are the principal findings in infancy. In older children the incidence of convulsions decreases and these are rarely observed in adults.

DR. THELANDER.—How much overall impairment follows these encephalitides? Are not the results much better than in the demyelinizing encephalitides which follow the acute contagious diseases?

DR. KOKERNOT.—Only about 1 or 2 per cent of our patients show residual impairment but this is the first time that such follow-up studies have been

undertaken and this matter requires further investigation. Such a figure is, of course, quite in contrast to the situation which applies to the demyelinizing encephalitides and to Japanese B virus or Eastern equine virus.

DR. PERRY.—What is the difference in the incubation period between St. Louis and Western virus?

DR. LONGSHORE.—Experimentally there seems to be none.

DR. PEARL KONTTAS.—Are these diseases self-limited or do they sometimes progress over a long period of time?

DR. LONGSHORE.—So far as I know they are strictly self-limited and get well with supportive treatment alone. We know of no specific therapy. Hyperimmune serum is used in horses but was not thought to be effective after the appearance of clinical symptoms and has not been used in human beings. These patients either get well or die, and I know of no instance in which the illness was protracted, recurred, or relapsed.

DR. LOUISE YEAZELL.—I have known of two patients who died with unexplained acute illness and at autopsy were found to have a chronic form of encephalitis but in these the etiology was not accurately determined.

DR. LONGSHORE.—We have seen patients who were considered to have cerebrovascular accidents who were proved to have rising titers later on. Whether encephalitis may have been concurrent with a cerebrovascular accident or not could not be determined.

DR. SHAW.—We had one patient who had been thoroughly exposed to insect spray containing lindane, chlordane, and the dilutant in which these were carried, became violently ill and until the late result of serologic studies proved the viral agent we were uncertain whether we dealt with a chemical encephalitis or an infectious process.

DR. LEVIN.—Actually we had two such cases. One was a 4-year-old child and one was a young adult. Both had a history of intensive exposure to insect sprays.

DR. SHAW.—But not quite soon enough to prevent the real etiology—exposure to mosquitoes.

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Psychologic Aspects of Pediatrics

EMOTIONAL ASPECTS OF RHEUMATIC FEVER IN CHILDREN

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EMOTIONAL factors have long been considered to be of importance in chronic illness, but the extent of this importance has been difficult to evaluate. To obtain a clearer picture of the role emotional factors play in such an illness, a team of investigators at the Massachusetts General Hospital has studied a group of twenty children with rheumatic fever and their mothers over a period of a year and a half.

The team was composed of four part-time psychiatrists, a psychiatric social worker, and a part-time psychologist. Two of the psychiatrists and the social worker interviewed sixty-eight mothers and children at the time of their appointments at the Rheumatic Fever Clinic. Some of these children had been seen only once a year in the Rheumatic Fever Clinic, others once every week or two. Their cooperation was solicited on the basis that the investigators were interested in knowing about the experience of the patients and their families with the hope that the illness might be made easier for others. The only criteria for selecting patients were that they be between the ages of 5 and 17 years, live in the Greater Boston area, and have had a diagnosis made at one time of rheumatic fever with or without heart disease.

In the group of twenty discussed here, nine of the children had rheumatic fever with heart disease, three had rheumatic fever without heart disease, and in eight a diagnosis of rheumatic fever was suspected but never confirmed. As the study progressed it became apparent that the group without heart disease did not differ appreciably from the others in its psychological reactions since all twenty of the children had been treated at one time as if they actually had heart disease. There were eleven boys and nine girls, all of whose medical records were reviewed and the diagnoses rechecked by Dr. Gertrud Reyersbach of the Children's Medical Service of the Massachusetts General Hospital.

Of the sixty-eight mothers approached originally, only forty-three were interested in entering the study and of these only twenty maintained enough interest to continue throughout the eighteen months of study. In general, the children were first seen in the Rheumatic Fever Clinic. Three of them, however, were interviewed while they were still hospitalized.

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The latter continued in the project after their discharge and return home. For the most part both mother and child were seen weekly for hourly interviews, the mother being seen by the social worker while the child was being seen by the doctor. An average of 19.3 hours was spent with each mother and 16.8 hours with each child. Nineteen of the twenty cases chosen were followed for over a year with five coming to the hospital weekly. In addition to this, five other children with rheumatic fever histories were seen for an average of seven hours each. The mothers of these children did not come in for one reason or another and hence they were not included in the study.

PROCEDURES

Before the main study was started a pilot study was carried out on twenty children with rheumatic fever at a near-by convalescent hospital by another psychiatrist and the psychologist. Twenty children on the orthopedic wards of another hospital were used as controls. Three areas were studied:

1. The effect of the illness upon the attitude of the child toward himself.
2. The effect of the illness upon the attitude of the child toward his parents and his feelings about their attitude toward him.
3. The attitude of the child toward medical care, hospital, doctors, and nurses.

This study led the investigators to conclude that the most important way to gain accurate information from such children was by establishing a good relationship with each child. The two hours spent with each child in this preliminary study were not enough to establish such a relationship. This was emphasized when one of the children, after he had come to know the psychiatrist well in the main study, said in reference to his earlier experience in the pilot group: "I told that other doc just what he wanted me to when he asked me all those questions. Us kids knew it was the best way to get it over with." He went on to relate how he and the other kids got together "to dope out the right answers for that guy."

A. *Psychiatric Approach.*—The psychiatrist's first aim was to establish a relationship with the child. This was done by using play situations involving toys or games suitable to the child. During the early interviews the conversations were nondirective with the child leading the way. After he had grown to trust the doctor, the latter pointed the play and discussion toward the illness, the hospitalization, the separation from parents, and feelings about rheumatic fever. Often such things did not come up until after ten to fifteen hours of interviews.

B. *Social Worker's Approach.*—The social worker, like the psychiatrist, used an indirect technique in her interviews with the mothers. However, when the illness of the child was brought up the worker encouraged a discussion of the subject. She often had to make a consistent effort to focus attention on the child and the mother's feelings about his illness, as the mothers tended to use the situation to discuss their own problems. As time went on, the research aspects of the case work often gave way to a more typical social worker-client relationship in the face of practical difficulties which arose. In such cases the worker often helped the mothers with outside problems in an attempt to keep the relationship firm. This activity helped

the mothers produce more material and was a factor in surmounting the difficulties which arose from the fact that their cooperation had been solicited by the project and that they did not originally come for help themselves.

C. *Psychologist.*—Objective material about the child's psychological processes was obtained by a battery of tests administered by the child psychologist. The tests included the Wechsler Intelligence Scale for Children, the Rosenzweig Picture Frustration study, the Rorschach test and the Draw-A-Person test.

THE MOTHERS

The mothers who joined this study were self-selected as most of them seemed to have emotional needs which they felt the project would meet. In addition to those who sought help in handling their children, there were those who sought help for themselves. Their attitude toward their problems had been such that none of them had ever sought psychiatric assistance nor had any of them been referred for such assistance from the Rheumatic Fever Clinic. With mothers who were unable to tolerate the psychiatric approach, the contact with the study was intermittent and frequently could not be maintained for more than a few interviews. Other mothers whose problems were unusually severe were so threatened by the study that they were unable to go on after the first interview.

1. *Relationship With the Child Prior to Illness.*—The mothers' relationship to their children prior to the onset of rheumatic fever was of prime importance in determining subsequent handling of the total illness situation.

An example of this is a mother who had her first and only child at the age of 45. His arrival was unexpected and unwelcome since her marriage had been strained for some years by her husband's constant infidelity and incompatibility. From the beginning, therefore, this mother felt resentment toward her small son. She viewed him as an additional burden on her already unpleasant life, yet compensated for this feeling with oversolicitude. This resulted in constant struggles between them during the first three years of his life, with the mother projecting her negative feelings about her husband onto the child. This hostility in turn gave rise to guilt in her. When the boy developed rheumatic fever and the doctors insisted that he be hospitalized, the mother was overwhelmed by these feelings. She felt she was responsible for his illness. This made it impossible for her to give him up to someone else's care, and she busied herself making amends for what she thought she had done by "curing him at home." Thus for the next two years she fought to keep him out of the hospital, and during this period their stormy relationship became even worse, with daily battles over his behavior. At the same time she brought out in her interviews that she should not have kept him at home in bed but should have hospitalized him as the doctors wished. "If only I hadn't kept him home all that time he wouldn't be so bad now."

This case and others like it illustrate how a disturbed pre-illness relationship of mother and child produces a disturbance in handling the illness. Another instance occurred in a family where the favored son was suspected of having developed rheumatic fever. Even though there was little objective evidence to substantiate this, the

mother insisted upon having him hospitalized at once. After his hospital stay which failed to confirm the diagnosis, she supervised his every move, insisted that he take long rest periods daily and prevented him from participating in sports even though the doctors specifically said he could.

When the rheumatic fever brought out the already existent difficulties between mother and child, the mother could then blame the illness as being the cause of their troubles. This happened again and again even though the material clearly showed that the pre-illness relationship had been a turbulent one. The mothers, however, repressed this.

In the instances where there had apparently been a good parent-child relationship prior to illness, the mothers also felt the child's personality had changed owing to the rheumatic fever. However, these mothers were able to accept the changes and help the child to adjust to them.

2. *Concept of the Origin of the Illness.*—No two mothers had the same concept of the origin of rheumatic fever despite the similarity of what the doctors told them. Their ideas varied according to many factors, some of which were correlated. These included:

a. The amount of information given by the doctors as to the cause of the disease.

b. Past experience with rheumatic fever in their own families, and hearsay from relatives and friends.

c. Concepts resulting from unconscious conflicts within the mothers.

(a) *Information from doctors:* The doctors were, of necessity, vague in their explanation of the origin of the disease. This vagueness acted upon the mothers in different ways. In some instances it caused a minimum of anxiety and the mothers merely regretted the lack of definite information, expressing confidence in the available treatment. In other instances it marshalled tremendous anxiety and forced the mothers to put considerable pressure on the doctors for more specific information. The more specific the information, the less threatening it appeared to be. When they were told that the origin was unknown and uncertain, they would come out with such statements as: "My doctor told me you got it from a cold," or "The doctors up in the clinic said it was a germ."

In common with most mothers of sick children, those mothers who developed anxiety about the origin of the illness sought external causes to blame, the most frequent being the cold and the damp. Eleven of the twenty mothers brought these factors up as not only being connected with the origin of the illness but also with its recurrences. Over two-thirds of the cancellations for appointments in the study were due to the mothers' telephoning that the weather was too cold or too wet and they feared their child might suffer a relapse if he went outside.

(b) *Past experience with rheumatic fever in own family:* Since there was a history of rheumatic fever or rheumatic heart disease in eleven of the twenty cases studied, many mothers had ideas about the origin of the illness which predated the birth of their children. This of itself is not peculiar to rheumatic fever but is found in any chronic illness whose origin is obscure such as diabetes or rheumatoid arthritis. One such mother attributed

rheumatic fever to accidents and cited as an example her sister who "fell off a pier one day and the next day she got rheumatic fever." She then linked this with her son: "That's how Eddy got sick. His foot was run over by a car and that was an awful shock. Shocks cause heart trouble."

Another mother who had developed rheumatic fever with heart disease at the age of 14 was convinced that her son inherited his rheumatic fever from her. "How could he help but get it when I've been sick all my life?" she asked. This concept of inheritance was especially strong in the families with multiple experiences with the disease, even though the mother herself might never have been sick.

(c) *Concepts resulting from unconscious conflicts and needs within the mothers:* In common with most parents these mothers developed guilt feelings about sickness in their children. Rheumatic fever, however, presents a more complex picture than other illnesses because of its obscure origin and recurrent nature. Perhaps because of this these mothers blame themselves more than usual for having allowed the children to become ill. Thirteen of twenty mothers were able to verbalize this directly, and the remainder said so indirectly, voicing their guilt in different ways. For example, one mother stated, "Laura would never have gotten rheumatic fever if I hadn't let her catch poison ivy the day before." Another said, "I let my child run around naked all summer long. He caught rheumatic fever from that." A third blamed the child with the comment, "He should have obeyed me when I told him not to go out in the rain."

Each mother handled her guilt according to her own personality make-up and background. Some attempted to manage their feelings by overconcern for the sick child, occasionally at the expense of the well ones as in the case of the mother who said, "We saw to it that Mary got the food the Rheumatic Fever Clinic recommended even though the rest of us had to go without."

One mother told how her son had wanted a bike very much though the father had been opposed to his having it. Despite the father's objections the mother bought the bike. Soon after that the father developed cancer of the throat and died within the year. Three months later the youngster came in following a bike ride complaining of aches in his legs. Rheumatic fever was diagnosed and the mother's explanation of the origin of the disease was, "I suppose he'd have been okay except for the bike." Here guilt over having countered the dead husband's wishes influenced the mother's concept of the origin of the illness.

3. *The Concept of Rheumatic Fever.*—The mothers presented many concepts of the nature of rheumatic fever. Each mother interpreted the process in her own way, with the ideas and accompanying fantasies having their origins in her past experiences. Three examples seemed to show this: At the time one child Joe developed rheumatic fever, the possibility of chorea was mentioned to his mother. "When they said to watch for chorea it scared me stiff," she said, "because I knew two ladies who weren't bright who had it and maybe this means Joe isn't bright." Throughout the time she took part in the study she indicated frequently how mental deficiency had become equated in her

mind with rheumatic fever and chorea.

A second mother and her twin brother had rheumatic fever with heart disease, and the brother died from it just before the patient Jim was born. Subsequently Jim developed rheumatic fever without heart disease. His mother believed firmly that rheumatic fever meant heart disease and an early death. In fact she described Jim as being "born with heart disease," despite medical evidence to the contrary. Discussion of her feelings about this brought out her early attachment to her brother who had dominated her entire life.

Finally, a third mother who appeared to be one of the best adjusted in the study linked her concept of the illness to her experience with her husband. The latter had rheumatic heart disease and was emotionally disturbed. During the course of the study he died under circumstances which suggested suicide. The mother felt he must have been insane because "only insane people kill themselves." She then became terrified that her daughter Louise would become insane too, since she felt that insanity was in some way linked to rheumatic fever. She projected numerous difficulties on Louise which were characteristic of her husband. For instance, when Louise had trouble with her eyes, she said, "My husband had eye trouble which gave headaches. It was all part of being nervous." She would then attempt to convince herself that her husband's death had been due to a heart attack.

Much of the confusion surrounding the concept of the disease seemed to stem from the mothers' inability to accept the doctor's explanation of the disease process. Nineteen of the twenty mothers kept asking the investigators, "Just what is rheumatic fever?" This was in spite of the fact that they had apparently asked the same question of numerous other doctors and other workers in the field.

Part of all concepts of the illness were ideas that since it involved the heart it meant death. Fifteen of the twenty mothers stressed the fear of death in connection with the disease. One doctor sought to alleviate a mother's concern in this area by showing her the child's heart through a fluoroscope. Her reaction was, "I'd never seen anything but a chicken's heart before and Jane's heart looked so big it frightened me." This led to unnecessary restrictions on the child for the first time because of the mother's anxiety over the incident. Discussion of her attitude toward this child indicated that she had always feared the child was not "normal." Apprehension centered predominantly about her size, maturity, and eating habits, anxieties which she did not have about her younger child.

Almost all the mothers in the discussions would use the word "heart" with more meaning than ordinarily. Their preoccupation was shown by remarks such as, "It frightened the heart out of me" or "I felt so low in the heart."

4. *Hospitalization.*—Of the patients included in this study, fourteen went away for care. In most instances the mother made the decision whether a child would stay at home or go away once the doctors recommended hospitalization. In instances where the child was hospitalized she was forced to assume the role of a rejecting parent. This added an extra burden to

such a decision. One mother described a violent conflict with her husband, ending in her taking the 6-year-old son away to the hospital during the day when the husband was at work. The father continually reminded the child thereafter of how the mother had been responsible for sending him away.

Another 8-year-old child was placed away from home against her father's wishes, but only after the mother had worn herself out trying to care for her at home. "I could never sleep through a night when she was sick because I was always afraid that she would need something and hurt herself trying to get it." This child and her father were very close to each other. The day she was transferred to the hospital, the father had a psychotic episode. Many of his thoughts centered on his guilt at feeling he was the cause of her hospitalization.

The mothers interpreted a recommendation for hospitalization according to their individual needs. Those who had the greatest difficulty allowing their children to be placed were the ones who had a neurotic need for their child to depend on them. Most mothers were able to prepare a child for separation from home and let him go away with a minimal amount of conflict, since they realized that it was impossible for them to give him the necessary care. Those who had difficulty in releasing their children were often able to do so after a period of home care had proved to be too difficult for them.

It sometimes appeared as though the mother felt that the doctors thought she had been a "bad mother" in that she had allowed her child to become ill; therefore she had to keep him home and give him exquisite care to prove she could be a "good mother." In some instances this feeling led to an intense need to prove her worth and a mother would give her sick child all the attention she had previously spread among her other children. "I never left Susan day or night. Whenever she was lonesome I would go and lie on her bed. She got the best food there was even though the others had to go without." Some mothers felt compelled to refuse hospitalization because they could not stand the pressure from the children to keep them at home. The pressure was usually in terms of the child accusing the mother of not loving him enough. Then it was necessary for her to prove her love and interest by keeping him at home and by overindulging him. Once the decision to hospitalize the child had been made, however, the mother seemed to feel relieved of some of her guilt and anxiety over his sickness. She was able to transfer a good deal of her concern over her child's welfare to the hospital staff and to feel assured that the case was under control.

Although the parents had mixed feelings about their forced separation from their ill child, in every instance but one they based the final reason for placement on medical needs. In this one case the mother said, "We thought it would be good to get her away from home for a while. We hoped they would teach her good manners, and not to be sassy to her mother." After she returned home from placement the mother said, "It was a lovely place. They taught her to wash her hair."

5. *Convalescence and Return Home.*—The mothers who kept their children at home seemed to have the

greatest difficulty in allowing the children to become mobilized. They tended to center their interests on them after any need for overprotection existed. One mother, whose 16-year-old son had been kept at home, laid out his clothes each day in the convalescent period to be sure he was dressed warmly and would not catch cold. Several years later another was constantly reminding her child to wear rubbers lest he become sick again.

The coming home of the hospitalized child seemed to affirm in the mother's mind that he was better and hence could return to normal activity safely. For one thing the mothers were glad to have their children back because their homecoming marked an end to the anxiety-provoking separation. The return also ushered in the beginning of what the mothers could consider recovery.

On the other hand, this could be overshadowed by the fear of recurrence which was usually emphasized by those in charge of the case. The mother's anxiety resulted in restrictions which were inexplicable to the child, as in the case of 10-year-old Joe whose mother said, "I don't dare allow Joe to ride his bicycle. The streets around our house have so many cars." She later admitted, however, that she could allow her other children to ride their bikes and she really worried that Joe might "drop dead" from his rheumatic fever. Another mother, who worked to support her family, said, "I need to keep Fred home from school next winter because he is so helpful looking after the younger children while I work." Subsequently, she confided that her real reason for keeping her son home from school (despite the clinic's recommendation that he attend) was that she was afraid of his getting an infection there with recurrence of his rheumatic fever. This mother was proud of the fact that the boy stayed in bed every Sunday and usually one or two days a week, "whenever he felt tired."

In general, problems which arose when a child came home were reactivations of old difficulties between him and the parents with a new intensity. One mother had always preferred her son George to her daughter Jane. After Jane returned home following hospitalization the mother blamed the illness for all previous difficulties she had had with her. At the same time she indicated she had always preferred George and had found him easier to take care of long before Jane became sick. Still another mother who had always been markedly hostile to her 11-year-old daughter would lean out the window to scream at her, "Don't skip rope, Margaret, or you'll drop dead."

The children provided new problems on their return by making excessive demands on the family as if they were seeking retribution for having been exiled. These demands were frequently difficult to meet, especially when they conflicted with other members of the family. One child, for example, was not supposed to walk upstairs and the mother was told he had to be carried. This added attention made his two healthy siblings jealous. His mother solved the conflict by carrying all three children up four flights.

Another aspect of the convalescent period was seen in those children who had been placed in a medical foster home instead of the hospital. In two

such instances the children developed warm ties to their foster parents which was threatening to their real parents on return home. To combat this the mothers did everything they could to make their homes like that of the foster parents. One family moved to another house and chose it "because it had a porch around it like the one at Mrs. Murphy's." The other mother allowed her son to eat gigantic amounts of food whenever he wanted to because "he told me that Mrs. Jones used to let him eat all the time."

6. *Reactions to Illness.*—Those mothers who were themselves the most disturbed handled their children's rheumatic fever with the greatest anxiety for the child. The mothers used the ever-present danger of recurrence and the other aspects of the disease in a way that suited their own neurotic needs in handling the child. A mother, whose 14-year-old son was suspected of having rheumatic fever, insisted on having him sleep with her because "Dickie might have a heart attack in the night." This mother's husband had deserted her and her only other son had been killed in World War II. She apparently utilized the rheumatic fever to keep the remaining child near her constantly.

"John has been sick and we can't expect as much from him," explained a mother whose son was a constant truant from school and was unable to pass in his school work. Although this boy had had rheumatic fever, he had never developed heart trouble but his mother continually stressed the condition of his heart. She explained that her own heart had been severely damaged by rheumatic fever when she was a child. She seemed to be treating him as the cripple she visualized herself to be.

There were other cases in which rheumatic fever was suspected but never confirmed. These children were treated as sick by the mothers who clung to the diagnosis. By contrast, other mothers who had less anxiety could give their child considerable reassurance by sharing their knowledge or lack of knowledge with him in a less threatening way. Apparently there was no correlation between the amount of anxiety a mother had and the actual severity of the illness in the child. Many mothers whose children had few symptoms reacted far more strongly than the mothers of the sickest children. In turn the ability of the parents to handle their own anxiety reflected itself in the child's ability to handle his illness. All too often the mother's feeling of bewilderment and loneliness in managing her problems showed itself in the child's own reactions. "My mother seemed so scared, I got scared, too," said one little girl.

7. *Recommendations in Working With the Mothers.*—It seems important that the medical team discover what the diagnosis and suggested treatment mean to each mother from the time she first hears about the illness throughout the subsequent months. From the moment of the first diagnosis, one person should be in continuous contact with the mother. The importance of the continuity of contact cannot be overrated. Mother after mother would say, "We saw so many different people," or "We'd just get used to someone when they'd change and we'd have to begin all over again."

Perhaps the most important contact with the doctor is the first one, when he tells the mother of the diagnosis. At this time after she has talked with him she would have an opportunity to discuss her feelings more extensively with a social worker. The latter, in cooperation with the doctor, could evaluate what aspects of the illness situation this parent could accept, with particular attention to the mother's concerns. Later, the same social worker could talk with the mother about subsequent plans for the child, and attempt to help her with the doctor's recommendations for care. By this time she would know the mother well enough to evaluate her reactions and, if necessary, steer her to further psychological help.

In this manner, the mother could be helped in preparing the child to meet the various pitfalls the illness presents. The question of hospitalization and the meaning of separation would be worked through for the parent as each step is taken. From the experience gained in this study it would seem that such casework could alleviate the guilty feelings which arise from the mother's having sent the child away, as well as her overreactions to other aspects of the problem, such as undue concern about recurrence and restrictions on the child's activities. Equally important is helping the mother in handling the difficult transition from hospital care to home convalescence. The worker could prepare the mother in advance for her role in this phase of the illness and support her emotionally throughout the long and trying period. Many mothers voiced the complaint that so often they had no one to turn to and they "didn't know what to do," thereby expressing their desire for such help.

From the social worker's viewpoint in this study, one of the most impressive findings was the real relief expressed by the mothers in discussing their feelings about the most threatening aspects of the disease. Many of these mothers, because of their inner reserve and apparent capability in dealing with their emotions, were never referred to a social worker at any time during their child's illness. The uniformity of their appreciation for the help given by the study showed that contact with a social worker could be of great value to all parents of chronically ill children.

THE CHILDREN

The work with the children produced material which closely paralleled that brought out by the mothers and helped to demonstrate how closely knit the mother-child unit had been in its reactions to the illness and its attendant anxieties. Whereas the mothers could eventually verbalize some of their feelings, the children were rarely able to express themselves as directly. For them a play situation was an easier medium of expression than words, but even this indirect expression of their underlying feelings was only possible after becoming confident of the doctor as a friend. At that point the play became more meaningful and could be directed toward areas which revealed the children's true feelings about the disease and the aspects of it about which they were concerned.

1. *Relationship to Parents Prior to Illness.*—The investigators felt that

the relationship of the child to the parents before the illness greatly influenced the way he subsequently handled his disease. This is well illustrated by a 16-year-old boy whose mother had overprotected him even prior to illness because of her fear that he would develop heart disease such as his father had. When he actually did contract a mild case of rheumatic fever, his reactions were out of all proportion to the illness and continued to be so long after he was well. Instead of running upstairs he would walk. Instead of going out to play with the other boys after lunch he would rest for a full hour, and so on. It seemed clear that he had actually developed a neurosis with anxiety attacks and constant fear of death.

The mother's handling of her anxiety at the time she was informed about the child's illness was important. Grace, an 11-year-old girl, said, "When I saw my Mommy was scared, I became real scared 'cos I knew it must be bad." A similar type of communicated anxiety was seen in war experiences by Anna Freud[5] and could be correlated with the degree of anxiety in the grownups around the children rather than with the severity of the actual situation. In the present study a 14-year-old boy, in whom the doctors did not make a diagnosis of rheumatic fever but mentioned that they were "ruling it out," remembers that his mother collapsed and wept. He was terrified and said, "I knew something was wrong with my heart. It pounded so hard." Thereafter his mother often brought up rheumatic fever to him despite the fact that the diagnosis was not confirmed and that the doctors assured his mother he did not have heart disease. His mother continued to think of him as a cardiac cripple. The boy's statement was, "I'll never be able to be a carpenter like my father. Every time I get up on a ladder my heart pounds away and I get too dizzy."

By contrast was a mother who had always had an excellent relationship with her 9-year-old daughter Laura. When Laura was brought to the hospital in cardiac failure the mother asked to be allowed some time alone with her "to explain what was going to happen." In the next half hour she explained how she would have to leave her for a while and the fact that she would come back to see her often. Although Laura wept for a while she was able to gain strength from the fact that her mother wanted to come back to see her all the time and had told her what to expect. Subsequently when something happened in the course of her treatment for which her mother had prepared her, Laura would brighten and repeat with some pride, "My Mommy told me this would happen."

2. *Concept of the Origin of Rheumatic Fever.*—Nearly all children develop a good deal of guilt over having become ill and express it in different ways. These ways often determined the child's concept of the origin of his illness, a reaction not at all peculiar to rheumatic fever. Many expressed the idea that the illness was a punishment for their wicked deeds or thoughts. An 11-year-old boy said: "I stayed out playing in the rain after the baby sitter told me to come in. My mother says that's why I caught rheumatic fever."

Some bodily inadequacy or weakness appeared over and over again as

a basis for the child's explanation of why he contracted the disease. A 10-year-old boy who had spent nearly five years in the hospital, flatly stated, "Those that get rheumatic fever must have a weakness in the first place." Turning to the doctor he then inquired anxiously, "Is it a germ that eats inside you and decays like losing a kidney?" This was symbolic of his fear of mutilation which was predominant in his make-up.

Still others blamed their parents, especially when the relationship between them had been a disturbed one. Eight-year-old Laura, who was involved in an intense oedipal situation with her father and whose mother had rejected her prior to her illness, played out some of her feelings with a set of dolls. At the start the mother and father dolls were on the floor lying next to each other. Then the little girl doll came forcibly between them, and the mother was taken upstairs to bed with a "heart attack." The little girl in turn had to be quickly sent off to the hospital because she was "sicker than her mother, as she had rheumatic fever."

When the mothers or doctors were able to give the child an explanation about the origin of the disease which did not imply responsibility on his part, the youngster was freed of a good deal of anxiety. This in turn seemed to enable him to adjust more easily to the disease. Conversely, it seemed that a child who suffered deeply from guilt attributed to the disease might handle the disease poorly, whether consciously or unconsciously. The 8-year-old girl above had a difficult convalescence in the hospital and, when she seemed to be improving, she began to rebel openly, got out of bed too early, and in general seemed consciously to interfere with her own progress. Though her problems were intense, it seems possible that the mechanisms involved might be applicable to less disturbed children.

The guilt which follows the anger at parents for their desertion in the hospital in chronic illness could be seen in those few who were seen in the hospital.[13]

3. *Concept of the Illness.*—The children's concept of rheumatic fever and rheumatic heart disease was difficult to investigate primarily because of their strong defenses. They seemed to fear talking about it and, if the subject was brought up too early, would often close up for several interviews.

Each child's concept of rheumatic fever was as vague as the mother's. Among the children who verbalized their fears well was an 11-year-old who became sad and pensive when the doctor brought up the question of rheumatic fever. She stated, "It's so awful to have it hanging over you. Maybe some day you'll have it again. It's terrible. I knew that it was heart trouble because they came to my house just to listen to my heart and never looked at my tonsils or anything like that. I thought it was something like chicken pox—contagious. The other girls would be afraid of you because it was contagious. When they found out it wasn't, they would either feel sorry for you and make you angry, or they wouldn't be sorry enough and then they wouldn't want to see you because there was something wrong."

Other children looked upon the illness in different ways. "Rheumatic fever is just like polio," one of the older girls told the doctor. "You don't know if you'll get it or not. It's mysterious. The boy across the street had it. It didn't leave me a cripple, though, like polio does. That boy had one leg shorter than the other." She laughed and explained that rheumatic fever is "aches and pains. It means being in bed. I didn't think it was much of anything 'cause I thought they knew what they were doing. They said it would take a long time to heal. You've just got to take things easy with lots of rest. If you don't you might get sick and get it again or get heart trouble."

It was in this often expressed fear of heart trouble that many children felt most anxious. Their anxiety was frequently heightened by the classification of potential rheumatic heart disease. They expressed the feeling that being followed in the Cardiac Clinic meant that they must have heart trouble. Although they strove to conceal their underlying fears occasionally they would come out with a statement like that of Gerry, who at the age of 10 had severe cardiac damage and told the doctor, "My grandfather had a shock so he was brought to the Massachusetts General Hospital. They kept him from dying of the shock. If you have heart trouble and have a shock you die. My grandfather collects stamps and so do I."

The concept of heart trouble was a difficult one for the child to grasp although each one knew it as a crippling lesion. A 9-year-old boy, who had spent three years in the hospital and who was still in the second grade, said, "When my heart trouble comes back again I guess I'll be put back another year in school." Later he asked, "What can a guy do who has a weak pump?" Fear of death was equated to fears of mutilation and of being different.

4. *Hospitalization.*—Of the seventeen children who had been hospitalized, four were seen while they were still in the hospital. When first contacted these patients had little to say, but as their confidence in the doctor grew a great deal of material came out. One boy, aged 10, said in his first interview, "The days really fly past fast." Later on when he had gotten to know the doctor better he said, "I felt I was never going to get out of the hospital." This same patient in the beginning had no derogatory comments to make about either the doctors or the nurses. In his eighth interview when he had been discharged, he said, "I don't look back at the hospital at all. I just don't want to think about it, especially the old nurses. They break your toys and bother you a lot. They make you do all sorts of things and get in your way." In his tenth interview he said, "The doctors don't know much. They thought you liked it there; I hated it!" This same patient later on managed to bring out that he was never given much information about his sickness. "Nobody told me nothing. One day I heard two docs say I had rheumatic fever. They just made things up. They're crazy." He elaborated on this by saying that he felt the doctors kept him in the hospital because there weren't enough other sick children to fill the beds.

Another boy, aged 16, recalling his life in the hospital when he was 7 said, "The nurses kissed us all goodnight. There was candy in a big can and four

boys in a room." He went on to say that he always wanted to go home but "I never said nothing to nobody about this. I figured I probably couldn't go anyway. I thought I might be there forever." Like many of the other children one of his principal dislikes of the hospital was "sticking needles in my arm" and another was staying in bed. He, along with most of the children, emphasized the hospital's insistence on watching their time up. He felt that they used this as a kind of weapon and resented this technique. "They keep you in bed longer if they don't like you or what you do."

These children often equate the duration and severity of their rheumatic fever to their badness in the hospital. "I got out of bed once when I wasn't supposed to, and the next day they said I was worse and put me in a room by myself. That's when I really got sick." The restrictions which were placed on them in the name of their heart disease seemed to impress them as much as any actual concept of the disease itself, and constantly reminded them of their illness.

Often in this disease, pressure is put on the child to eat. Improvement is often equated with appetite, or, as is more often the case, to the patient's willingness to eat in spite of severe anorexia. An example of what this sort of pressure means to a child was shown by an 11-year-old boy with severe heart damage, who said, "I knew I would have heart trouble. The nurses told me I'd never get well if I didn't eat. Instead I threw the food out the window when they weren't looking. I'm bound to have heart trouble."

The necessity for putting pressure on children to adhere to restrictions became a source of conflict. The passive children seemed to interpret the restrictions as punishment rather than as measures necessary for their well-being. The more active children rebelled against the restrictions but in so doing appeared anxious. Their bravado broke down all too easily in the interviews. As one 11-year-old said: "If I act scared, then I ain't got a chance. Them docs will slap on all they can. They got my Ma scared but not me. Sure, I got something wrong, but that don't mean it's quits—not yet, anyway."

Separation from home was expressed as the most serious aspect of the hospitalization. This was often necessary in an acutely ill child without adequate preparation. Inability to understand this formed him to find reasons for the sudden removal from home. Eight-year-old Lucia elaborated about why hospitalization was necessary in her case and how it became a further form of punishment for her misdeeds. In a play interview she brought her doll to the doctor, saying: "Dolly's been sick four weeks with a cold and a temperature. She's had rheumatic fever before. It was mild but the doctors said she had a heart murmur. They didn't tell her what that was, just told her it was something wrong with her heart. She was in the hospital a short time—a few months—as she wasn't very sick, and they said she got over it okay. But I was always afraid of this, that she'd catch another cold and get it all over again. Dolly's such a bad girl. She always does what I tell her not to do; she never wears her rubbers."

Doctor: "Is it Dolly's fault she got sick?"

Lucia: "Oh, no, it's her mother's. She should have made her wear her

rubbers, but she didn't. Now if she should be sent to the hospital you send her. She'll get better there. Anyway I can't keep her here. She's too much of a brat. She never minds me. Keep her there a good long time so she'll be a good girl when she gets home. I don't want her home. She's too bad at home and I've got a boy at home who's good."

Doctor: "What if you don't come and get her?"

Lucia: "She can just go to an orphan asylum. The doctors don't want her if she's well: no one wants her if she's sick."

Doctor: "But she's been in 6 months already. That's a long time to a little girl like Dolly."

Lucia turned to the doctor and said earnestly, "I hated being in. I was in for a whole year, too. No one came to get me."

This feeling of desertion by the parents constantly recurred in each child's recollections of the hospital stay. The child's need for dependence on his parents to support him under such a stress situation is well understood. Separation from them at such a time amounts to a weakening of the child's capacity to deal with the problems of adaptation, and his anxiety about the separation and about the illness becomes increased. The nurse, doctor, or attendant can function as a parental substitute, but visits, letters, and real contacts with home are essential to the child. Frequent visits by the parents during hospitalization do much to overcome this feeling of desertion and enable him to handle his illness better. The crying which follows such visits is often felt by some to be detrimental to the child's condition. From an emotional standpoint this crying may serve as a valuable release for his misery. The attempt to suppress such feelings is a real drain on his resources, and it appeared that the longer the interval between visits the more emotion the child had to release.

5. *Convalescence and Return Home.*—Following discharge from the hospital with its limiting environment, the child often burst forth in a surge of activity when he reached home. This proved to be upsetting to the mother who was cautioned about the restrictions she must place on the child, and, in her apprehension, she reacted to his behavior by imposing even more restrictions. To a child who has longed to come home for many months and envisaged a life free from regulation, this reaction was both baffling and disappointing. On the other hand, overindulgence on the mother's part may be upsetting to the patient, who feels he must be sick indeed to be treated in such a fashion. This overprotection augments his fear of being damaged or different because of the rheumatic fever. One child defiantly said: "They won't spank me; they wouldn't dare. I've been sick." At the same time she expressed her anxiety about the parents' change in attitude toward her. One can guess what abolition of discipline accompanying this overprotection might mean to a growing child.

Again, the anxiety implied in the changed treatment was a source of concern to the child. The extent of the anxiety is expressed in a 9-year-old boy's remark, "Now that I'm home again the outside world seems sort of strange, and a lot bigger than I remembered it. My mother says I've got to rest a lot and get big and strong before I can go out and play again."

The children who were kept at home for their convalescence seemed to fall into a rather homogeneous group. They expressed fears which were tied directly to their parents' overprotectiveness. In general they were a passive, dependent group. Their rebellion, which might have expressed itself against the hospital and personnel, had to be quelled in home convalescence. It had to be expressed in subtler, less open ways. For example, there was the 8-year-old who "led her parents around by their noses because she'd been sick and if they didn't give in to her she'd kick and scream and cry and get sick all over again."

The returns to the Rheumatic Fever Clinic for checkups seemed to frighten them all. They were afraid of the bad news of recurrence and the fear of being suddenly hospitalized again.

Visits to the therapists of the study assumed the same significance. A 9-year-old girl expressed her feelings as follows, "What am I coming here for? Are you going to give me tests with needles and things, or are you just going to watch me to see what's wrong? They never tell you anything at the Rheumatic Fever Clinic either. They don't tell you what they are going to do. They block your eyes and say you won't feel it. (Going on to a doll) She hates hospitals. She does feel it, but they tell her she's not going to. Open your mouth wide so I can pull your teeth out. They're not going to tell her anything about what they're going to do and then they're going to pull her teeth out. They forced her to take her aspirin. She hated them. But they made her better. She doesn't have heart trouble though. I don't hear a thing. Now she's practically well. Let's close the case."

6. *Reactions to the Illness.*—Any severe illness such as rheumatic fever with its implications of heart damage seems to serve as a real trauma which lowers the capacity of each child to withstand the tension of day-to-day living and separation from his family. However, rheumatic fever seems particularly hard to endure because of its constant threat of recurrence and the possibility of death. In these respects it is much like cancer and one is struck with the remarkable similarities between the findings in the current study and those reported by Shands and associates.[10] They stated that "The difference in behavior and affective state of patients with psychoneuroses and those with somatic illnesses are largely differences in the intensity and duration of certain observable phenomena rather than differences in kind."

In those children whose prior adjustment to life had been an effective one, the reaction to rheumatic fever was minimal, whereas in those children who had previously shown evidence of emotional disturbance, the reaction was more marked. Between these two appeared to be a group which developed a type of reaction under severe stress that Ferenczi[3] called a "patho-neurosis."

As in any stress situation the patients reacted with various adaptive mechanisms with varying degrees of success. The particular type of adaptation chosen, as Fenichel[2] among others has pointed out, "depends, of course, on the total structure of the personality, its history, and its latent defense struggles." The following were the principal types of reactions found.

Denial: This was one of the commonest defenses. An insecure 10-year-

old boy, whose family was made up of six sisters, mother, and alcoholic father, said, "I ain't never been sick." This was despite the fact that he had spent nearly four years of his life in the hospital. Seeming to find some explanation for his comment he went on to say, "The docs just made it up. I guess they needed kids for the hospital."

Regression: Eight-year-old Charlie typified this reaction. He had always been bullied by a hostile, overprotective mother who never allowed him to grow up. When he was put to bed he soon began acting like a child of 2 or 3 with baby talk, thumb-sucking, and infantile behavior. His was not an isolated case but something seen more in the hospital setting than afterward.

Identification: The study found children who relieved their anxiety about their illness by identifying with children who had been sick with rheumatic fever and had then become well. This was especially true in the hospital where frequent references were made to those patients who had gone home.

Another use of identification in handling anxiety aroused by the illness and the doctor as typifying the illness was by identifying with the aggressor. Several examples of this have already been seen wherein the child played doctor and performed tests on a doll similar to those she had experienced in the hospital and the Rheumatic Fever Clinic. This assumption of the controlling role instead of the passive one was of great comfort to the child.

Repression: An occasional child repressed all feelings about his illness. Elise, who had been in the hospital nearly sixteen months, kept answering the doctor's questions by saying, "I don't know" or "I don't remember." It was not until after she had been seen for over a year that she began to recall details of the hospital life and how badly she had felt there. During the early months of her interviews she appeared baffled by the doctor's interest in her illness and kept saying, "nothing ever happened in the hospital. There isn't anything to tell." Later on she recalled vividly how her radio was taken away as a punishment for overactivity, with her time up reduced for naughtiness, and how few and far between the visits were.

Isolation: As a defensive measure isolation appeared most frequently in the children's follow-up visits to the Rheumatic Fever Clinic. They would be given appointments and then simply not appear. This would often happen three or four times in a row. When questioned they might put the blame on the weather but more likely they would say, "Why should I go back there? It just reminds me that I'm sick and I don't want to hear about my rheumatic fever any more."

Sublimation: Only a few children were able to use this successful defensive reaction. A 13-year-old started drawing pictures of her dreams during the long months in bed at home. These seem to be closely linked with her fears and worries over the illness as seen in her interview material. When she recovered, her interest in art continued and finally she sought and obtained a scholarship in a local art school.

Whereas healthy children might have a basically optimistic attitude toward competition and punishment for being bad, these children were fatalistic and looked for punishment in terms of certain recurrence of disease.

One girl of 12 said, "I feel that if I don't do everything the does say I'll get sick again and that will be it. Then I'll never get big and marry like my sister." Competition with other children their own age was tinged with this same fatalism. Many of them seemed competitive on the surface but under a rather thin veneer one felt an incapacitating fear of losing which rendered them failure-prone. The threat of recurrence of the disease became symbolically associated with punishment for any successful aggressive approach on the part of the child. George, 10 years old, said, "I wanted to pitch in our ball game the next day when that night I woke up and had a pain in my elbow. I guess that is when my rheumatic fever started."

Some children make conscious use of the illness. Roberta, an 8-year-old girl, typified this when she said, "I make my father do what I want him to. When he won't I just grab my chest. He knows I might die any time!" A less conscious use of the illness for secondary gain seemed to be present in George, who had many "false alarms" in his hospital record. Along with two prolonged hospitalizations for active rheumatic fever, he was admitted overnight to the emergency ward on six different occasions for a question of recurrence of his disease. All tests proved negative and his mother pointed out that each episode followed some failure in school or with his contemporaries. He was a passive boy who refused to compete in school with his classmates, or in checkers with his therapist. When he did win, he became anxious and wanted to play another game to lose. His fatalism about recurrence of rheumatic fever was in the same vein.

There did not seem to be anything peculiar to rheumatic fever patients in the use of these defense mechanisms. Any sick person, as Freud[6] pointed out, "relinquishes his interest in things of the outside world." The somatic process occupies his entire interest, and his handling of it reflects many factors in his background and personality.

In this study the conclusions drawn by Josselyn[7] in her paper on rheumatic fever were borne out. Rheumatic fever seemed to add pressures and anxieties to an already existent weak psychic structure.

7. *Recommendations for the Children.*—It is of advantage to a child with rheumatic fever to have someone, preferably a parent, stand by and explain as much as possible what is going to happen to him. The details of hospital life and the procedures he may expect can be elaborated upon. Later the child finds security in his parent and the memory of having been prepared. Each new event reminds him of his parent's explanation for it and gives him comfort. The doctors and nurses have a responsibility to give the parents information so that they in turn can pass it on to the child. Likewise the various members of the hospital can act as substitute parental figures for the child. Warm, sympathetic, and flexible nursing personnel can alleviate the double psychological trauma of (1) the loss of parents, and (2) the guilty feelings brought out in the child by having become ill.

The realistic difficulties and restrictions of rheumatic fever seemed less crippling than the fantasied ones. Realism, however bad, has a more reassuring quality for children than the fear of the unknown. Talking to a

child about his illness is reassuring to him. An understanding doctor encourages ventilation of these fears, anxieties, and questions from the child. This leaves a valuable bond for communication. The child can then express his anxieties as the illness and convalescence progress. It greatly facilitates helping him to deal with them as they arise.

The admitting procedures can be conducted in a friendly fashion, and parents can be urged to bring in a child's favorite toy, to write him post cards, and bring him reminders of home. In making recommendations for the hospitalized children one must consider the need for restrictions imposed by the limitations in any hospital. The investigators feel strongly that more frequent visiting by the parents would do much to overcome feelings of desertion. Since abandonment was the principal trauma leading to these children's neurotic difficulties, one would be striking at the very source of their troubles by promoting continuous contact with their parents who are their main source of strength. Many hospital personnel feel that the crying which follows parental visits is detrimental to the child's condition. From an emotional standpoint, however, this crying serves as a valuable release for the child's miseries. It is his method of dealing with his inner feelings of desertion and rejection. His attempts to suppress such feelings are a real drain on his resources.

Often the children interpreted as punishment their being kept in bed, having needles or necessary procedures or having their "time up" taken away. This is helped by sympathetic explanations from the doctor or nurse as to the need for restrictions which did not imply criticism of the child.

A normal child's mischievousness and restless impulses usually find an outlet in aggressive play. He is deprived of these outlets in a confining illness like rheumatic fever. Unless constructive ways are found to deal with this energy it may build up to a level difficult for the child to handle. His response to this is frequently to withdraw or regress. If this accumulated energy could be directed into acceptable channels, such as group play or even group therapy by a psychotherapist, these deleterious reactions would be by-passed. This in turn would decrease later reactions to his hospital experience and make him less fearful of recurrences with their attendant hospitalizations.

The isolation of a newly admitted child for twenty-four hours can be traumatic. The frightened child who feels guilty and deserted has to endure a period of isolation in which he can enlarge upon his fears and loneliness. This may set the stage for regression and withdrawal. These are severely debilitating to the child's total personality and may do him permanent damage psychologically.

Finally, it is important to have a constant person in the hospital to whom he can turn to ventilate his grievances, fears, and fantasies. This will make the child feel that he is not deserted. Such a person would serve as a liaison between him and the outside world. He will thus be better able to resume his place in it when his illness is over.

The child must be prepared for his return home and for the restrictions which will prove necessary. Otherwise he will be disappointed be-

cause he is not able to lead a normal life immediately. Again, it is important to emphasize the need for these restrictions without implying criticism of the child. Factual explanation of the disease and the chance of its recurrence must be given. This can be done without suggesting constant impending disaster. A child can flourish emotionally despite a crippling physical disease, if he is given reassurance in an understanding way.

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Comments on Current Literature

INFANTILE ECZEMA

THE over-all management of patients with infantile eczema presents serious problems, all too well known to those who are engaged in pediatric practice. In consequence, any form of therapy which offers promise of beneficial results in such patients is eagerly sought after both by the physician in charge of the patient and by the unfortunate parents. When steroid therapy, cortisone or adrenocorticotropin (ACTH), was shown to bring about spectacular temporary improvement in infantile eczema, considerable enthusiasm was expressed concerning the usefulness and possibilities of this new addition to the already rather extensive list of therapeutic adjuncts in the treatment of this condition. However, the parenteral administration of these steroids requires expensive hospitalization, and in the majority of cases, therapy must be continued over a relatively long period of time in order to maintain the favorable action. Likewise, the complex and often serious side effects of steroid therapy under these circumstances may present difficulties which are quite formidable.

In fact, Lewis Webb Hill[1] has concluded from his own experience and that stated by others, that "these agents when given parenterally and in a hospital . . . have little place in the practical over-all management of the disease," in spite of their apparent favorable effect. Nevertheless, this author is not willing to eliminate the use of steroids from his therapeutic regimen, but has sought rather to investigate the efficacy of the steroids by oral route in the treatment of infantile eczema.

In a report entitled "Oral Cortisone Treatment of Infantile Eczema," which was published in *The New England Journal of Medicine*,[1] issue of June 18, 1953, Hill reviews his experience with oral cortisone in the treatment of eighteen children with infantile eczema, all under the age of 3 years. Most of the cases were severe, some of them having done very poorly under the usual methods of therapy. Six patients were under the age of 6 months; five were between 6 months and 1 year of age; and seven were between 1 and 3 years. Duration of treatment varied: three patients were under treatment for a period of from one to two and one-half months, thirteen patients, a period of three to six months; in the case of one patient, treatment was continued over a period of eleven months. All patients received potassium chloride, 0.3 Gm. (5 gr.) twice daily; antibiotics were not administered routinely but were given whenever there was the slightest suggestion of skin infection or respiratory infection. The dosage of cortisone by mouth was kept at the minimum amount just required to relieve the eczema, but in dosage which would do no harm to the child when continued over a long period. In order to avoid if possible the development of serious side effects, the maximum daily dose was not allowed to exceed 75 mg. of cortisone. This rule was followed rigidly in all cases, except one. In addition to cortisone, all eighteen children were given the benefit of the usual supportive care for eczematous patients. The results of this study are classified by the author as follows:

Group A	Results unsatisfactory	4 cases
Group B	Results superior	8 cases
Group C	Results worth while, but not superior	6 cases

The case histories of all eighteen patients are reviewed in detail. In the four patients of Group A, in whom results were considered unsatisfactory, it is of interest that two were described as suffering from severe nummular

eczema (coin-shaped lesions), a type of eczema which is extremely difficult to treat, and in which, as a rule, the patient does not respond well to any form of therapy. In the case of one of these patients, the dosage of cortisone was increased from the recommended 75 mg. daily to 100 mg. per day, and eventually to 150 mg. per day. Although the child's severe eczema did improve temporarily on this regimen, acute potassium deficiency with cardiac manifestations developed, and clinical signs of stupor and extreme prostration were evident. While cortisone did appear in this case to reduce loss of serum from the lesions, and to keep the lesions relatively dry, the patient's over-all eczematous condition was not altered significantly, and the dosage of cortisone necessary brought on serious side effects.

Another patient described under Group-A classification was a 5-month-old infant with eczema of a severe erythrodermic type who developed a typical Cushing syndrome on a dosage schedule which was never allowed to exceed 75 mg. daily, and in fact, was reduced to 25 mg. daily. Results in this case were good so far as the dramatic improvement of the eczema was concerned, but completely unsatisfactory in general, since the dosage of cortisone needed for maintaining the improvement also produced side effects characteristic of the Cushing syndrome.

In the second group (B), eight cases were reported as showing superior results. In these patients cortisone by mouth was valuable in controlling severe exacerbation of generalized eczema during seasonal prevalence of antigenic substances such as tree pollens. In these cases, classified for the most part as atopic dermatitis, the response to cortisone in daily doses of from 75 to 25 mg. was favorable. In most instances the skin showed dramatic improvement in seven to ten days, and improvement was maintained on gradually diminishing doses for periods of six weeks to five months. Care must be exercised in the reduction of dosage since too rapid decrease often resulted in exacerbation of the skin condition, necessitating a return to higher dosage level. In most instances the cortisone was reduced gradually, and the general improvement was excellent.

Group C, where results were considered worth while but not superior, included six patients. In general, the children in this group responded favorably to oral cortisone. However, in order to keep the eczematous condition under control, doses of cortisone larger than 75 mg. daily were required, and, as is emphasized by the author, considerable clinical judgment was necessary with reference to the amount administered, the duration of treatment, prevention or control of untoward side effects, etc. Patients were under close observation, and each one was individualized carefully.

On the basis of these studies the author concludes that cortisone in daily oral doses constitutes a valuable addition to the usual local and immunologic treatment for children with severe eczema. However, he stresses the fact that steroid therapy is symptomatic treatment only, and that it is advisable to ascertain individually the smallest possible dosage regime which will keep the eczema under moderately good control, the child relatively comfortable, and the parents satisfied. Hill believes that the total daily dose administered should never exceed 75 mg., and that a much smaller total daily dose is preferable. His experience with the one patient in whom the Cushing syndrome developed emphasizes the need for careful evaluation of the individual clinical response even to relatively small amounts of steroid substance. Accordingly, Hill's recommendation is to initiate therapy with 75 mg. per day, and, as soon as possible, to lower the dosage gradually by stepwise reductions of 12.5 mg. until a level is reached which just brings about favorable changes in the eczematous state, but which does not produce serious side effects. Usually ther-

apy must be continued for periods of weeks or even months, and when the hormone is to be discontinued, withdrawal must be gradual even where the total daily dose is already minimal.

The routine use of antibiotics is not recommended, but rather that vigilance should be constant for the appearance of possible skin or pulmonary infection, or of other signs of infection, in which event appropriate antibiotic therapy can be instituted. The author concludes his discussion of the serious therapeutic problem involved in most cases of eczema in children by recommending that steroid therapy be reserved for severe cases only, and that duration of treatment with steroid substances be as short as possible—only that required to relieve an immediately distressing situation.

In this very interesting presentation, Hill succeeds in outlining a reasonable approach to the problem as to whether steroid therapy is indicated in the treatment of infantile eczema. Although the present series is small (eighteen cases), Hill's report provides a guide which should be of considerable value in helping the practicing pediatrician to make intelligent and effective use of a powerful therapeutic agent, and at the same time to avoid its accompanying serious untoward side manifestations. If it can be shown that daily oral cortisone in a dosage sufficient to relieve infantile eczema does no harm to the child when continued over relatively long periods of time, such therapy would be indeed welcome as an adjunct to the usual local and immunologic forms of therapy available in this distressing clinical syndrome.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Ann Arbor, Mich., June 26, 27, and 28, 1953.

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The next oral examinations will be held by the Board at: Miami, Fla., Oct. 9, 10, and 11, 1953; Indianapolis, Ind., Dec. 4, 5, and 6, 1953.

At the Annual Meeting of the **Section on Pediatrics of the A. M. A.** at New York in June, the following officers were elected for the ensuing year: Chairman, Dr. Oliver L. Stringfield, Stamford, Conn.; Vice Chairman, Dr. William W. Belford, San Diego, Calif.; Secretary, Dr. Wyman C. Cole, Detroit, Mich. Dr. F. Thomas Mitchell of Memphis was re-elected as representative to the Scientific Exhibit, and Dr. Hugh Dwyer of Kansas City, custodian of the Jacobi Fund. Dr. W. C. Crawford of Rockford, Ill., was elected section delegate, and Dr. Walter B. Stewart of Atlantic City, alternate delegate to the House of Delegates of the A. M. A. A total of 799 registered for the section on pediatrics out of a total registration of 17,958.

The **Bureau for Handicapped Children** of the **New York City Department of Health** has recently issued a report on "Recommended Standards for Audiology Centers." The bureau was assisted by an advisory committee headed by Dr. John F. Daly, professor of otolaryngology at the New York University College of Medicine. The report goes into such questions as the function of an auditory center, the per-

sonnel and their qualifications, and the physical equipment and setup.

The **Endocrine Society** and the **University of Minnesota** announce a Postgraduate Assembly in Endocrinology and Metabolism for Physicians, the Sixth Annual Assembly sponsored by The Endocrine Society, which will be presented on the University of Minnesota campus from Sept. 28 to Oct. 3, 1953. Lectures will be held in the Museum of Natural History Auditorium, while the facilities of the immediately adjacent Center for Continuation Study will be available for demonstrations and for the accommodation of registrants for the course. All aspects of clinical endocrinology and metabolism will be taken up, and recent important advances in the field will be stressed. Informative demonstrations and illustrative clinical cases will be presented, and ten panel discussions will provide registrants with opportunities to bring up special problems and questions. Each registrant will receive a booklet containing abstracts of all lectures. Faculty for the Assembly includes outstanding authorities in the field of endocrinology from various parts of the country as well as members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The program will be presented under the direction of Dr. Edward C. Reifenstein, Jr., General Chairman for The Endocrine Society, and Dr. C. J. Watson, Professor and Head, Department of Medicine. Chairman of Local Arrangements on behalf of The Endocrine Society is Dr. Edmund B. Flink.

A portrait of Dr. Tom Mitchell, Professor of Pediatrics, University of Tennessee and Chief of Staff of the Le Bonheur Children's Hospital, was presented to the University of Tennessee June 11, 1953, in honor of his many years of service in the division of pediatrics. The portrait was hung in the conference room of the Le Bonheur Children's Hospital.

Dr. Benjamin Spock, 3811 O'Hara Street, Pittsburgh 13, is revising *Baby and Child Care* and requests suggestions from pediatricians.

Are any sections misleading and worry parents instead of reassuring them? Without increasing the length of the book, should some material be dispensed with and some be added? Would it be better to list only one simple evaporated milk formula with or without sugar? Has the section on premature infants been helpful except to reassure expectant mothers in far-off places?

Book Reviews

Modern Concepts of Communicable Disease. Morris Greenberg, M.D., and Anna V. Matz, R.N., New York, 1953, G. P. Putnam's Sons, 553 pages.

Dr. Greenberg, Director of the Bureau of Preventable Diseases of the New York City Department of Health, and Mrs. Matz, Nursing Consultant in Communicable Diseases to the Department, have collaborated in writing this text on the present-day concepts of communicable disease. Both have drawn on a wide experience in the field and as teachers. It is not an exhaustive text for the scientist, but rather the material is presented in a way that will be useful not only to students and physicians but to auxiliary workers in the public health field as nurses.

Part I of the text considers the "Basic Principles of Communicable Disease." A first interesting chapter traces the various concepts that have been held from primitive to contemporary times. The second discusses community control through worldwide, national, and local organizations. Other chapters in this section discuss epidemiology, treatment in a general way, medical asepsis, hospital management, and the problems of communicable disease nursing in the home.

Part II—roughly three-fourths of the text—discusses specific diseases. In all, fifty-four communicable diseases are discussed, grouped into those transmitted by respiratory discharges, food and water, contact, and the anthropods. Naturally there is more interest in and much more to be said of some than of others. Thus diseases like poliomyelitis and tuberculosis are discussed at length while many of lesser importance from a public health standpoint are briefly treated. Emphasis in discussion has ob-

viously been placed on the diseases which have been problems in New York City, while the tropical communicable diseases are only summarized. This, however, does not detract from the text so far as its usefulness in this country is concerned. In general, each disease is discussed as to the causative agent, the host (symptoms, diagnosis, immunity), the environment, and medical care plans (treatment, diet, nursing).

The nursing care discussion for many of the specific communicable diseases is somewhat repetitious—"supportive," "relieving discomfort"—although these terms describe about all that can be done or is needed. When more detailed, they are occasionally far fetched, as, for example, stressing psychologic factors in measles, "children who suddenly erupt with measles develop anxieties about the cosmetic effect of the rash." Most are far too sick to worry about this and the rash fades too rapidly. The general discussion of communicable disease nursing is excellent, but the authors evidently were hard put to carry out the discussion for each particular disease. It is impossible to discuss the many topics considered in the book in a detailed way in a review. As a whole, the presentation and discussion are excellent and the authors have succeeded in putting a tremendous amount of material in a brief, dependable, and readable form.

Congenital Anomalies of the Heart and Great Vessels. Maurice A. Schnitker, New York, 1952, Oxford University Press, 306 pages.

This book adds very little to the available literature on congenital heart disease. The section on embryology and morphology, however, is quite good and easy to follow. The remainder of the book is composed of the usual congenital cardiac defects which are encountered in most medical centers. The book merely represents a moderately thorough review of the available literature but very little in the way of critical interpretation by the author.

DAVID GOLDRING, M.D.

Clinical Orthopaedics. Anthony F. DePalma, Editor-in-Chief, Philadelphia, 1953, J. B. Lippincott Co., 242 pages. Price $6.00.

This is the first of what the publisher terms a series of books rather than a journal to be published about twice yearly. Approximately the first two-thirds of this volume contains fifteen articles in the field of pediatric orthopedics, and the remainder, articles on general orthopedic conditions. Many of the articles are decidedly sketchy in character. Among the pediatric conditions discussed are arthritis, early roentgenologic changes in Perthes' disease, scurvy, which is hardly an orthopedic condition, femoral shaft and supracondylar fractures, and scoliosis. The most interesting discussion for the pediatrician is that of posture by Goff. It is not planned to present a section on pediatric orthopedics in each volume.

Reducing Emotional Trauma in Hospitalized Children. 1953, Departments of Pediatrics and Anesthesiology, Albany Medical College, 82 pages.

This is a report on the three-year study of reducing emotional trauma in children hospitalized for tonsillectomy. Several chapters are reprints of articles which have appeared previously in medical journals. To these an introductory statement as to the scope and method of the study and a summary by Dr. Faust have been added. The study shows that the most important factor in reducing trauma from hospitalization lies in humanizing the hospital routine and procedures, and in trying to give the child an explanation of the experience he is about to go through. Thus the pediatrician who knows the child and parents, and who advises the operation, is perhaps the most important link. Some particular procedures as rectal temperature, enemas, and injections are pointed out as repelling to the child and hence should be avoided.

Blum-Fieldsteel Development Charts. New York, 1953, World Book Company.

These are two charts for plotting the development of motor and functional behavior of a child from birth to 6 years of age, based on the Gesell schedules of development. Only one or two of the various characteristics of development for a specific age are used in plotting the graph. The charts will be useful in enabling the pediatrician to record in an objective graph the development and progress of an infant in whom retardation is obvious or suspected.

Editor's Column

THE DISTRIBUTION OF POLIO IN THE UNITED STATES

THE validity of statistics for the incidence of a disease depends upon the reliability of the reporting. The reporting of measles, for example, is poor, although there is no diagnostic difficulty, and the true incidence is considered as several times that reported. Polio is another disease in which there is considerable question as to the validity of incidence statistics. The reason here, however, is that doubt as to the reliability of reporting is due to diagnostic difficulties, rather than apathy or carelessness on the part of the physician. There is every reason to believe that during the polio season many cases of infection with the polio virus occur which produce no specific symptoms or signs which make a definite diagnosis of polio possible. On the other hand, when polio is present, many cases are diagnosed and reported as polio which turn out to be something else. For example, the diagnosis was wrong in 409 (28.9 per cent) of 1,420 patients admitted with a diagnosis of polio to the Philadelphia Hospital for Contagious Diseases in the ten-year period 1940 to 1949.[1] Even with these limitations on the reported incidence of polio representing the true incidence, reported statistics over a long period of time make fairly valid information available for the comparison of the incidence in different parts of the country, as the errors in reporting are in all probability fairly uniform. Although the first epidemic in the United States occurred in Vermont in 1894, it was not until 1910 that an effort was started to have polio made a reportable disease, and it was not until 1922 that this was achieved on a nationwide scale.

In a recent article, Serfling and Sherman[2] present an interesting report on the distribution of polio in the United States, plotted for five-year periods for the last twenty years, 1932 to 1952. From 1932 to 1944 the annual national reported rate did not exceed ten cases per 100,000 of population. From then on the reported rate steadily increased until it reached 36.9 per 100,000 in 1952. Some of this increase, in our opinion, may have been due to better reporting, resulting from more interest in the disease and the development of "polio hysteria," as it has been termed, but unquestionably the true incidence has increased.

The distribution for the five-year periods is shown in the accompanying graph, which we have reproduced with the kind permission of the editor of *Public Health Reports*. The authors feel that their figures do not reflect a consistent geographical localization. In the ten-year period, 1932 to 1941, there was a fairly uniform incidence reported of 5.1 to 5.9 per 100,000 of population in five of the nine geographic divisions, with the lowest rates in the West South Central, and South Atlantic states, and the highest rates in the Mountain and Pacific states (6.3 and 10.7). In the first five years of the next decade (1942 to 1946), the rates in the West North Central, Mountain, and Pacific states were higher than those for the Southern part of the country. In the next five-year period the divisions west of the Mississippi had rates consistently higher than those east of the river, and the increase in the West South Central states over the three previous five-year periods was striking. While geographic difference in rates have

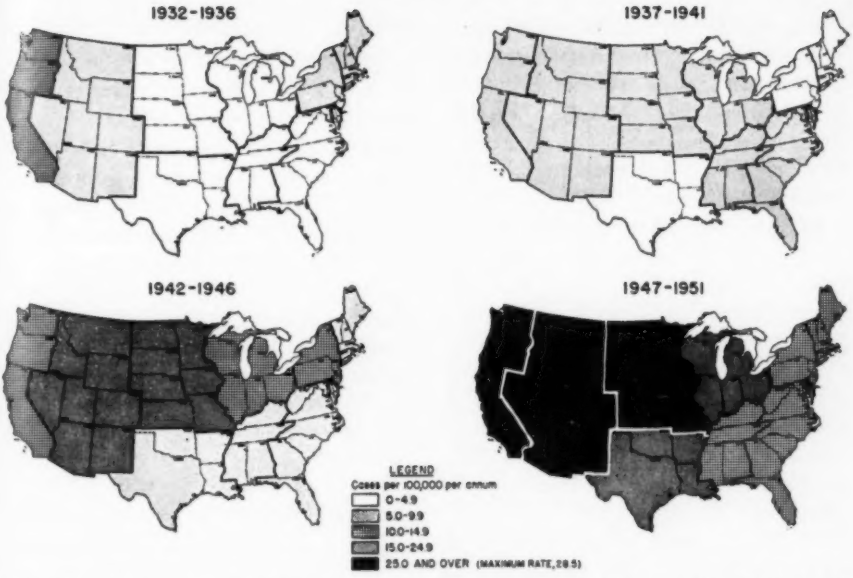

Fig. 1.—Poliomyelitis morbidity—average five-year rates, major geographic divisions of the United States, 1932-1936, 1937-1941, 1942-1946, 1947-1951. (From Serfling and Sherman: Pub. Health Rep., May, 1953.)

existed by years and periods, these differences over the years have tended to become equalized. This is shown in figures taken from one of their tables.

While the tendency in the long run is for the polio rates to equalize, the picture as to epidemics is a changing one from year to year. Thus the most severe outbreak in 1934 was on the Pacific Coast and in 1935 in New England. From 1940 to 1948 severe epidemics did not strike east and west of the Mississippi in the same year as a rule. In 1949 severe epidemics developed in all sections of the country except the South Atlantic states, and in 1950 rates were fairly high in all areas. In 1952 the epidemic in the West North Central states reached the highest rate recorded, and high rates were recorded for all sections of the country except New England and the Middle Atlantic states.

Thus there is a constantly changing picture in the distribution of polio each year, with a tendency to equalization over a period of twenty years. The Pacific states have had a fairly consistent high rate, which has also been true for the Mountain and West North Central states in the last decade.

DIVISION	10-YEAR MEAN		20-YEAR MEAN
	1932 THROUGH 1941	1942 THROUGH 1951	1932 THROUGH 1951
New England	5.9	11.4	8.6
Middle Atlantic	5.1	13.1	9.1
East North Central	5.1	15.7	10.4
South Atlantic	4.6	10.2	7.4
East South Central	5.2	10.1	7.7
West South Central	3.0	16.0	9.5
West North Central	5.5	23.7	14.6
Mountain	6.3	22.5	14.4
Pacific	10.7	20.1	15.4

The rise in the rate in recent years in the Southwestern states suggests to the authors that it may be of interest to watch the trend in the Southeastern states where the increase in the annual rate has been only moderate over the twenty-year period.

In this connection it is of interest to note the incidence as it has developed so far this year. For the entire United States in the seven weeks from June 1 to July 18 of this year (latest detailed figures available as this issue goes to press), 4,353 cases of polio were reported as compared with 4,455 in the same week period in 1952. However, the reported incidence in the South Atlantic states was 769 in 1953 as compared with 375 in 1952, and in the East South Central states was 533 as compared with 428. This is a 62 per cent increase for the Southeastern area. The two regions combined reported 30 per cent of the total cases reported in this seven-week period in 1953, as compared with 18 per cent of the total for the same weeks in 1952. Whether this increase both locally and in relation to the total number of cases for the year will continue for the remainder of the summer is unpredictable. As of August 1, the total reported incidence for this year is a little less than reported last year.

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1. Dawson, LaBoccetta, Tornay, and Silverstein, J. PEDIAT. 40: 71, 1952.
2. Serfling and Sherman: Pub. Health Rep. 68: 453, 1953.

DEATH FROM ACCIDENTAL POISONING

ON SEVERAL occasions during the past years the JOURNAL has commented editorially on accidental poisoning in young children (iron,[1, 2] aspirin,[3] and parathion[4]). We prefer to designate it as poisoning due to parental carelessness or ignorance. With the tremendous decrease in the IMR after the newborn period which has taken place in the last forty years, death from accidental poisoning has become a significant factor in the runabout child aged 1 to 4 years.

In a recent issue of the *Archives of Disease in Childhood*, Swinscow[5] of London discusses the deaths from accidental poisoning that have occurred in children aged 1 to 4 in England and Wales. In the ten-year period, 1940 to 1949, there were 218 reported deaths, not including those due to toxic gases. The rate for males under 5 years was considerably above the female rate, as is true for the incidence of injury in the home. The types of poisoning were as follows:

	No.	%
Medicaments	135	62
Household poisons	47	22
Disinfectants and antiseptics	15	7
Poisonous plants	8	4
Miscellaneous	13	6
	218	101

Thus nearly two-thirds were due to medicaments, either physician's prescriptions or preparations bought over the counter for internal or external use. The chief offenders and the number of deaths were: iron preparations 21, oil of wintergreen 17, strychnine 15, and aspirin and quinine 12 each. Among the less frequent offenders opium or morphine was responsible for 8 deaths, soporifics as phenobarbital 8, camphorated oil 5, and antihistamine drugs 5. A number were occasionally responsible, including ipecac, iodine, acetic acid, digitalis, antimony, and copper sulfate. Thus a long list of medicines left carelessly within reach of young children which caused accidental deaths.

Twelve of the 47 deaths from household poisons were due to caustic soda and 11 to phosphorus in rat poisons. Other deaths in this group were due to the hydrocarbons as kerosene and petrol, ammonia, nicotine, arsenic, and carbon tetrachloride.

Phenol and creosol caused 9 of the 15 deaths in the disinfectant and antiseptic group. Eleven of the deaths from poisonous plants were due to the nightshade weed, and only 1 to fungi. Hydrochloric acid was the chief cause of death in the miscellaneous group.

There is no reason to believe that the incidence is much less or greater per 100,000 of population in the United States. Assuming this, it would work out to around 900 deaths in runabout children from accidental poisoning in the United States in the same ten-year period. As Swinscow summarizes, "Accidental poisoning by ingestion of toxic substances, especially medicaments, is a notable cause of death in the age group 1 to 4 years."

Who is responsible? What can be done to prevent these unnecessary deaths? Direct responsibility lies with the parents of the runabout child who, as a normal phase of his development, learns by exploring and investigating at this age. But the blame cannot be placed entirely on their shoulders. An element of blame in some instances rests squarely on the physician who fails to warn parents that such ordinarily nondangerous drugs as aspirin and ferrous sulfate may cause fatal poisoning if accidentally taken in quantity by a young child. Another element rests on the manufacturers of these drugs which are sold without prescription over the counter, who fail to warn the purchaser of their danger. The poison warning on some of the rat poisons and insecticides is not sufficiently prominent or emphatic enough to impress many who become careless and leave these substances within reach of children. Perhaps it is a case of familiarity breeding contempt in some instances.

Certainly something can be done about it. First of all the medical profession—and the pediatricians should take the lead—should start a definite educational campaign to educate parents as to the potential danger of many drugs. Verbal education by the physician at the time the drug is prescribed will probably be more effectual than education by printed words. Warnings on labels should be more emphatic and prominent. To cite an example of what can be done: The two articles reporting ferrous sulfate poisoning in young children including two deaths, together with the editorial on the subject in the January, 1952, issue of the JOURNAL, were submitted in proof form to the national medical committee for Red Cross blood banks, before publication in the JOURNAL. The result was an immediate rewriting of the label on the iron tablet packages given to donors at the blood banks, carrying a prominent and emphatic warning as to their danger if ingested in quantity by a young child.

If physicians will take a definite stand on the matter, the pharmaceutical houses will fall into line. Further, such a stand will be reflected upon the Government agencies who control the labeling of commercial substances such as rat poisons and insecticides. We are quite sure no maker of these products will want to bear any of the responsibility for the death of a young child from accidental poisoning.

REFERENCES

1. 40: 141, 1952.
2. 41: 122, 1952.
3. 42: 276, 1953.
4. 42: 642, 1953.
5. 28: 26, 1953.

CURRENT PEDIATRIC REFERENCES

TWO years ago the JOURNAL took over the monthly publication of the *Current Pediatric References* which had been started a year previously by Dr. A. B. Schwartz of Milwaukee in mimeographed form. As stated at that time,* Dr. Schwartz would continue to edit the references, and they would be published without curtailing the average amount of text published in each volume of the JOURNAL.

At a recent meeting of the Editorial Board a question was asked as to how much use was made of the references by JOURNAL readers. No one was willing to hazard an opinion. As a result the Editor was asked to poll a cross section of subscribers. In June a letter was sent to 811 on the subscription list, with a return postcard with questions phrased to obtain the following desired information:

I. The number who use the references and want them continued.

II. The number who use the references but are indifferent as to their being continued.

III. The number who do not use the references and are indifferent as to their being continued.

The original plan was to poll every tenth name on the mailing list. This was found impractical from a mechanical standpoint, and so a selection by states or consecutive parts of states was used, covering every section of the country and including rural areas and areas with large medical centers. None were sent to the 2,000 foreign subscribers because of the time element for returns, and so the cross section represents approximately one in every nine subscribers in the United States and Canada.

The result of the questionnaire was as follows: 490, or 60 per cent, of the 811 sent out were returned. This, we are informed by "experts," is an unusually high return. Sixteen returns were discarded as commercial or incomplete. Of the 474 tabulated, 215 use the references and want them continued; 195 do not use them and are indifferent as to their being continued; 64 reported as making occasional use but were indifferent as to continuance. Thus, of the number returned, 45.4 per cent wanted the references continued and 54.6 per cent were indifferent. Even if we assume that most of the 40 per cent not returned was due to indifference, we calculate from the cross section poll that at least 3,000 subscribers use the references and want them continued. The Editorial Board thus finds the *Current Pediatric References* fill a definite need and the JOURNAL will continue to carry them.

It is of interest that the percentage division of the first fifty returns was almost exactly the same as in the final tabulation, and this held day by day as the returns came in although there was a marked difference in the return geographically. No distinct variation from the total percentages was found when the returns were classified by different sections of the country, or as by returns from rural areas as contrasted with those from cities with a large medical center.

The Editor wishes to express his thanks to those who answered the questionnaire.

*Editor's Column, J. PEDIAT. 39: 395, 1951.